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ADRENOCORTICAL HORMONE TREATMENT OF PULMONARY TUBERCULOSIS.¹By R. MUNRO FORD,
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In 1950 Hart and Rees,⁽¹⁾ and also Michael and his co-workers,⁽²⁾ reported that large doses of cortisone administered to mice simultaneously infected with tuberculosis appeared to cause an acute spread of the disease.

As a result, attention was focused on the dangers of using this agent in humans if they were also suffering from tuberculosis, healed or otherwise. In fact, several reports soon appeared in the literature confirming the inadvisability of administering cortisone or ACTH to patients suffering from various diseases such as rheumatoid arthritis and asthma, etc., with coexistent pulmonary tuberculosis.⁽³⁻⁵⁾

Further experimental studies carried out on rats, mice, rabbits and guinea-pigs produced contradictory evidence concerning the effect of these agents on new or established tuberculous infection.⁽⁶⁻¹⁷⁾ In most cases, however, large doses of cortisone appeared to exert an unfavourable

influence on tuberculous processes in these animals. Observations on the cornea of mice by phase contrast microscopy, and on rabbits by the ear-chamber technique, have shown that large doses of cortisone produce relatively constant changes in a tuberculous focus.⁽¹⁸⁻²¹⁾ First, the inflammatory process is quietened by a suppression of vascular dilatation and a reduction of cellular response to the infection, particularly leucocytes and macrophages. However, rapid bacillary multiplication also occurs, and areas of caseation and necrosis continue to extend. Dissemination of the tuberculous process throughout the body then proceeds steadily and kills the animals within a few weeks. It was noted, particularly by Ebert and Barclay,⁽¹⁹⁾ that when cortisone was stopped after a short period of administration the suppressed inflammatory reaction recurred almost immediately.

A few reports were published describing the results of actually treating tuberculosis in humans with cortisone and ACTH.⁽²²⁻²⁵⁾ These findings showed that, while the clinical condition of the majority of patients initially improved, their tuberculous disease either remained unaffected or deteriorated during treatment or soon after corticosteroid therapy was stopped. As a result it was recommended that the presence of tuberculosis represented a contraindication to the use of cortisone or ACTH.⁽²⁶⁻²⁷⁾

In the meantime, several workers were investigating the effect of cortisone or ACTH combined with specific chemotherapy on experimental tuberculosis in animals.^{(19) (110) (117) (38-42)}

¹ The bibliography to this paper has been omitted for reasons of space; it is obtainable from the author on request.

Once again results were varied; but in general it appeared that such a combination of treatment did not adversely affect the course of the disease. In fact, in many cases, tuberculous lesions appeared to be most favourably influenced by this therapy.

These findings led to a revision of thought concerning the use of these agents in humans, and it was recommended that if corticosteroid therapy was indicated for patients who were suffering from coexistent tuberculosis, then chemotherapy should be administered at the same time. In addition, these results stimulated a more critical appraisal of the possible place of corticosteroids in the actual treatment of tuberculous infection.

Reports began to appear describing the treatment of tuberculous meningitis with cortisone or corticotropin *plus* chemotherapy.⁽³²⁻³⁴⁾ These have shown that such patients, who do not respond promptly to standard chemotherapy, do very well when corticosteroids are added to their treatment regime for a few weeks.

The rationale of this treatment has been that these agents cause a lessening of the inflammatory reaction in the meninges, with a subsequent decrease in exudate and associated mechanical blockage caused by organizing fibrotic tissue. Tuberculous arteritis will also be suppressed, and as a result vascular damage giving rise to neurological sequelae will be lessened. In addition, the general resistance of the patient, lowered perhaps as a result of failure of the adrenal cortex to overcome the initial overwhelming toxic effects of the disease, is also boosted.

Most workers have reserved the use of cortisone and its allied compounds for patients with far advanced tuberculous meningitis not responding to chemotherapy, or with evidence of spinal block; many physicians, however, mainly in the European field, have used these agents for all patients with meningeal tuberculosis. Their published results have been very good; such excellent figures as a 97% total recovery rate have been reported by C. Cocchi.⁽⁴⁰⁾

It was natural that workers should turn to pulmonary tuberculosis for further investigations concerning the effects of a combination of chemotherapy and corticosteroids on this disease, especially if it was not responding to standard methods of treatment.

Several reports have been published in this regard,⁽³¹⁾⁽³²⁻³⁴⁾ although there has been a paucity of these compared with the actual number of trials being conducted in various parts of the world.

The results of earlier work, particularly in America, have suggested that a combination of corticosteroids and chemotherapy exerted only a temporary clinical benefit on tuberculosis sufferers. Other workers, however, have achieved good results both clinically and radiologically, especially in the treatment of far-advanced disease. In particular, the work of Houghton, of Cochran and also of Edge has shown that corticotropin or cortisone *plus* chemotherapy has effected marked clinical and radiological improvement in nearly all tuberculous patients so treated.

Apart from tuberculous meningitis and advanced pulmonary disease, a few similar trials, mainly by European workers, have been carried out in military and childhood tuberculosis and also in exudative pleurisy with effusion. Good results have been reported in nearly all cases in which cortisone has been employed for a few weeks with intensive long-term chemotherapy. Desensitization of patients hypersensitive to various antituberculosis drugs has also been successfully accomplished with the aid of cortisone or corticotropin.

Various hypotheses have been advanced to account for these good results in pulmonary tuberculosis. First, it has been suggested that there occurs a reduction of the acute inflammatory process and with it a diminution of the toxic side effects resulting from the infection; several workers have thought that this may aid easier permeation of specific antimicrobial agents into the inflammatory tissue and around the tubercle bacilli themselves. Secondly, it is believed that non-specific stress as a result of adrenal

exhaustion or atrophy may be relieved by cortisone replacing the associated steroid deficiency, or by ACTH stimulating the adrenal cortex to do so itself.

In review, it appears that despite various opinions to the contrary, there is no real evidence to hand that tuberculous disease in humans is adversely influenced by cortisone or ACTH therapy, if effective antituberculosis chemotherapy is also being administered at the same time.

Indications for the use of adrenocortical hormone therapy in the treatment of pulmonary tuberculosis are still undecided. However, its more generally accepted present-day status is well summarized in the following words of Katz and his co-workers:⁽⁴⁰⁾

... that without anticipating any change in the ultimate outcome, cortisone therapy would appear to be justified, if only for its symptomatic effect, in patients hopelessly ill with advanced tuberculosis.

THE PRESENT STUDY.

The present study analyses the results of the treatment of 12 patients, suffering from pulmonary tuberculosis, with adrenocortical steroid therapy *plus* specific chemotherapy.

This treatment has been given for two reasons. In the first group of eight patients all were suffering from far-advanced toxic disease and were being overwhelmed by this process. Their prognosis was regarded as hopeless; in fact, three patients receiving oxygen daily were not expected to live for more than a few days. Corticosteroids were added to chemotherapy in this group in an effort to reduce acute toxicity and to supplement a possibly failing adrenal cortex.

The second group of four patients were all suffering from chronic pulmonary tuberculosis of many years' standing, and despite apparently efficient long-term chemotherapy, were still "sputum-positive" and unsuitable for collapse or excisional measures. Corticosteroids were administered to these patients in an endeavour to aid chemotherapy in reaching inaccessible tubercle bacilli, perhaps by causing lysis of tenacious fibrotic tissue. Reactivation with increased vascularity of the disease processes, when corticosteroids were withdrawn, was also considered a possible factor in aiding their more effective concentration around tubercle bacilli.

Methods and Results.

Group I.

Group I consisted of eight patients suffering from far-advanced pulmonary tuberculosis which was deteriorating despite chemotherapy (two grammes of streptomycin, 900 milligrammes of INH and 12 grammes of PAS per day). All were extremely ill, with cough, copious sputum and a temperature of 100° F. or more, four weighed less than seven stone, and three were receiving oxygen daily; the prognosis appeared hopeless in each case.

In addition to clinical and chest X-ray studies, erythrocyte sedimentation rate and serum electrolyte estimations and drug sensitivity tests were performed on all patients before and at intervals during corticosteroid therapy.

Four patients received 40 units of ACTH daily for one week, but as none responded clinically, this was discontinued.

Two patients received cortisone in reducing doses from 50 milligrammes twice daily to five milligrammes twice daily given over ten days; but although both showed remarkable clinical improvement, relapse occurred in each case a few days after the administration of this agent had been discontinued.

Thus the eight patients in this group all received cortisone, 50 milligrammes twice daily, *plus* chemotherapy as outlined above, for periods ranging from six to eight months, except one who died after two months. Prednisolone, in a dosage of 10 milligrammes twice a day, was substituted for cortisone in all cases after about two months of therapy.

The initial response to this treatment was dramatic in every case, with considerable reduction in cough, sputum, pyrexia, erythrocyte sedimentation rate, and malaise. In

fact, cough and sputum had disappeared in four cases within two weeks. Appetite improved in all cases, and the average weight gain during the first month exceeded two stone.

At the end of the first two months of treatment cortisone therapy was stopped or reduced gradually. However, in each case cough, sputum, pyrexia and erythrocyte sedimentation rate increased rapidly, and weight loss and malaise returned within a few days as severely as or worse than before. After a few weeks of this continued deterioration the administration of cortisone, 50 milligrammes twice a day, was recommenced in all cases. Once again the patients' clinical condition and weight, etc., improved rapidly, with the exception of one patient suffering from bilateral cavitary pulmonary tuberculosis with associated tuberculous enteritis. He had been practically moribund before the commencement of cortisone therapy, with a history of illness of several years' duration, for which he had received various regimes of chemotherapy. Drug sensitivity studies before the administration of cortisone demonstrated tubercle bacilli in his sputum, highly resistant to streptomycin, INH and PAS; post-mortem examination revealed extensive ragged cavitation throughout both lungs and an atrophic adrenal cortex.

The remaining seven patients continued to feel well and were practically symptom-free during the next two months of treatment with corticosteroid *plus* chemotherapy. An attempt was then made to reduce gradually the amount of prednisolone which they were then receiving. However, all patients promptly relapsed again within a few days after prednisolone therapy was stopped, and it was found necessary to recommence it. All patients again showed considerable clinical improvement almost immediately.

At the end of six months' treatment, two patients, who remained symptom-free, showed almost complete radiological clearing of their disease; the dosage of prednisolone was gradually reduced at this stage. Both have remained well, with negative bacteriological findings and static chest X-ray appearances for three months now after corticosteroid therapy has been stopped; they are still continuing to receive chemotherapy. The medical status of these two patients was somewhat similar; each had a three months' history of clinical and radiological deterioration, despite intensive chemotherapy, of bilateral, extensive pulmonary tuberculosis which was mainly exudative in nature; neither had received chemotherapy previous to his present illness; also their sputum had contained tubercle bacilli which remained sensitive to streptomycin, INH and PAS whenever tested. These two patients were therefore able to dispense with corticosteroid therapy without any apparent ill effects. Either their lesions had been completely sterilized, or the chemotherapy which they were receiving was now adequate to keep their disease in check.

Of the five remaining patients in this group, two remained clinically well and maintained a low erythrocyte sedimentation rate, an increase in weight, an absence of cough and sputum, and radiological stability of extensive disease. When their corticosteroid therapy was stopped after six months, they relapsed clinically once more within a few days. Their pre-treatment status was also similar. Both had been suffering from pulmonary tuberculosis for several years and had received chemotherapy for varying periods during that time; both showed X-ray evidence of extensive fibrocavitary disease combined with exudative disease; the sputum of both contained tubercle bacilli resistant to PAS, moderately resistant to streptomycin and sensitive to INH. It appeared that after six months corticosteroids were still necessary to hold their disease in check, and that available chemotherapy alone was inadequate to do so.

The clinical status of the three remaining patients gradually deteriorated during the fifth and sixth months of corticosteroid therapy. They developed several bouts of pyrexia, recurring cough and sputum, loss of weight and increasing erythrocyte sedimentation rate during this period. All these particular patients were suffering from fibro-cavitary *plus* exudative disease; their sputum, prior to corticosteroid therapy, contained tubercle bacilli highly

resistant to streptomycin, INH and PAS. It appeared in these cases that, after four or five months, corticosteroids were losing their effectiveness in controlling the disease.

There was little overall evidence of toxicity from adrenocortical hormones, although three patients showed some evidence of salt retention, oedema of the ankles and "moon face"; but after a change was made to prednisolone, none of these side effects were seen. In several cases, however, when cortisone or prednisolone therapy was stopped, signs and symptoms of acute adrenal crises occurred, suggesting possible atrophy of the adrenal cortex as a result of corticosteroid therapy.

The net result of the treatment of patients with far-advanced, hopeless tuberculosis with adrenocortical hormones *plus* chemotherapy is as follows. Out of a total of eight cases, after six months, in two the disease appears to have been completely arrested and in two it appears to be controlled only by continuing the administration of these corticosteroids with chemotherapy; in three cases the disease appears to have been controlled for three to four months only; one patient died during therapy after two months. The best results were seen in those patients with a short history and suffering from mainly exudative disease, with sputum containing drug-sensitive tubercle bacilli. The worst results were seen in those suffering from acute or chronic fibro-cavitary disease with sputum containing drug-resistant tubercle bacilli; however, even in these cases corticosteroids appeared to prolong life for at least several months.

Group II.

Group II consisted of four patients suffering from chronic pulmonary tuberculosis; all had persistent tubercle bacilli in their sputum despite long-term chemotherapy; all were under the age of forty years and appeared destined to spend the rest of their lives in hospital or in isolation; two patients had low-grade pyrexia, and all had chronic cough with a moderate amount of sputum.

All showed radiological evidence of chronic fibro-caseous tuberculosis with one or more cavities. In addition, tubercle bacilli highly resistant to PAS and moderately resistant to both streptomycin and INH were present in the sputum of two patients, and tubercle bacilli moderately resistant to PAS and streptomycin and sensitive to INH were present in the sputum of the other two.

All patients were assessed before and during treatment, similarly to those in Group I.

In addition to previous chemotherapy, all patients had recently received at least six months' intensive chemotherapy—i.e., two grammes of streptomycin three times a week *plus* 900 milligrammes of INH and 12 grammes of PAS daily—without alteration of their radiological or bacteriological status.

Chemotherapy was discontinued in each case, and treatment with cortisone, 50 milligrammes twice a day, was commenced and continued for three weeks; cortisone was then withdrawn abruptly. During these weeks all patients improved considerably; cough, sputum and erythrocyte sedimentation rate were reduced, and the temperature returned to normal; an average of one and a half stone in weight was gained, and each patient said that he felt physically much better and mentally more alert. Chest X-ray appearances in all cases remained unchanged at the end of the three weeks.

One or two days after cortisone treatment was stopped, all patients developed pyrexia (temperature 100° to 101° F.), a return of cough and sputum, elevated erythrocyte sedimentation rate, and malaise; one patient developed a slight pleural effusion after one week.

At this stage (i.e., one week after cortisone therapy was stopped), the daily administration of streptomycin (two grammes), INH (900 milligrammes) and PAS (12 grammes) was begun for each patient. Two improved slightly during the following two weeks, but the other two appeared unaffected by this chemotherapy. During the following month all patients deteriorated clinically, with loss of weight, increasing pyrexia and cough, and sputum which

appeared to contain many more tubercle bacilli than before commencement of cortisone therapy. It was therefore thought necessary to recommence corticosteroid therapy and continue it for a longer period of time.

This was done, and the administration of prednisolone (10 milligrammes twice daily) plus chemotherapy was continued for a further two months. All patients once more improved clinically, and all felt well during this period. Chest X-ray appearances in all cases remained unchanged. At the end of this period the dosage of prednisolone was gradually reduced; however, two patients relapsed clinically when this had reached five milligrammes twice a day and the other two relapsed shortly after the administration of these agents was stopped. Two patients also developed acute withdrawal symptoms with low blood pressure and muscle cramps, etc. A small quantity of pyrazinamide was available, and this was given in a dosage of three grammes a day to one patient in addition to his other chemotherapy. The response after the first two weeks was good, and he has remained fairly well since, without corticosteroid therapy. Pyrazinamide therapy was stopped after six weeks, and this patient's clinical and radiological condition, after a further three months, was about the same as before corticosteroid therapy was first begun.

The status of the other three patients is as follows. After six months one is clinically well taking prednisolone, 10 milligrammes twice daily, plus streptomycin, two grammes thrice weekly, and INH, 900 milligrammes daily; his chest X-ray films have shown no change. However, every effort to wean him off corticosteroids has brought about a clinical relapse. The other two patients, during the last two months of this period, have commenced to deteriorate slightly, with the return of some cough and sputum and a gradual loss of weight and increasing erythrocyte sedimentation rate. The dosage of prednisolone was increased to 15 milligrammes twice a day in both cases and appeared to halt this deterioration in clinical status. These patients' chest X-ray films showed no change; but the sputum of both of them was then found to contain tubercle bacilli highly resistant to streptomycin and PAS and moderately resistant to INH.

One patient developed "moon face" after two months' cortisone treatment; otherwise no toxic side effects were seen.

After six months the net result of the treatment of chronic tuberculous disease with corticosteroids and later chemotherapy has been that the condition of one patient is approximately the same as before treatment commenced, but that the other three are in the unfortunate position of having to continue taking corticosteroids in order to prevent relapse. Also, in two of these corticosteroids appeared to be gradually losing their effectiveness.

This therapy cannot therefore be said to have improved the status of any one of these patients; in fact, the outlook for three has considerably worsened.

DISCUSSION.

During the past few years the world has seen tremendous progress in the treatment of pulmonary tuberculosis. Specific chemotherapy, combined with excisional surgery in particular, has fomented the hope that in almost every case this disease can be arrested, if not cured. Although this hope has not altogether been realized, there is no doubt that life has been prolonged, infectivity has been reduced, and the length of illness has been considerably shortened for nearly all tuberculous patients as a result of these measures. Recently, more and more attention has been devoted to a more direct frontal attack on the tubercle bacilli themselves by the use of more effective specific chemotherapy. The results appear to suggest that tubercle bacilli may be eradicated altogether from the lesions of a considerable percentage of patients so treated.

However, there are one or two factors which still undermine a confident expectation of good results from this treatment; one is the host-parasite relationship itself. Some sufferers appear to be overwhelmed by an apparently moderate infection, and despite the aid of intensive anti-

tuberculosis therapy, rapidly succumb to the over-all toxic effects of the disease process itself. In other words, it seems that there is a group of people whose defences are unable to deal with their tuberculosis. It has been suggested that the secret lies in the state of their adrenal cortex, a deficiency in which may cause a predisposition to tuberculous infection and an inability to cope adequately with that infection once it has been established. This type of patient apparently needs something in addition to our standard methods of treatment.

There is another unfortunate group of patients who are unresponsive to chemotherapy and unsuitable for collapse or excisional measures. This is often the result of inefficient or inadequate early treatment, or of a host tendency to combat infection by developing fibrosis, caseation and chronic cavitation etc. in disease areas. These patients with chronic disease often have persistent sputum containing tubercle bacilli wholly or partly resistant to the various antituberculosis agents available, and seem destined to spend the rest of their lives in hospital or in other isolated circumstances.

Two types of patients, therefore—the patient who is dying from the toxic effects of tuberculosis, and the patient with chronic infective disease—were selected in this trial to receive what is considered rather drastic and perhaps somewhat dangerous therapy. This we have been led to believe by early reports concerning the administration of adrenocortical hormones in the presence of active tuberculosis.

Over the past few years, however, the initial recommendation that the presence of tuberculosis is a contraindication to the use of adrenocortical hormone therapy has been gradually modified. First, it was recommended that such hormones should always be accompanied by adequate chemotherapy if given to patients suffering from coexistent tuberculosis. Later it was found that they appeared most useful in prolonging the lives of sufferers with far-advanced, hopeless tuberculosis, by controlling the toxic effects of their disease. Finally, rather more enthusiastic, particularly European, workers now incorporate these agents as a routine measure in the treatment of pleural effusion, meningeal tuberculosis and other acute types of tuberculous disease.

Thought concerning the mode of action of corticosteroids, as they are commonly called, has also undergone some metamorphosis. It was originally believed that cortisone would cause an actual spread of disease if given to tuberculous sufferers. Now it is considered that it actually reduces the inflammatory process, and that relapse or spread of infection tends to occur after their administration has been stopped. In addition, the almost feverish application of chemists to the task of synthesizing and purifying these agents has also inspired physicians with a confidence that toxic side effects such as salt retention etc. have been virtually eliminated.

In this trial there appears no doubt that all the acutely ill patients in Group I would have died from their tuberculous disease within a few weeks. Now, of a total of eight patients, two may have been completely cured, and two appear to have gained a fair chance of a further several years of life. At the very least, life in all patients appears to have been decidedly prolonged by the use of adrenocortical hormones.

Definite indications as to the possible success or otherwise of this method of treatment cannot be deduced from this small series of cases; but it does appear that the administration of adrenocortical hormones with chemotherapy may be given a good chance of achieving permanent success if the following criteria are fulfilled—i.e., if the patient is succumbing to the massiveness of his tuberculous infection perhaps as a result of a poorly functioning adrenal cortex, and if his disease is exudative in character and the infecting tubercle bacilli are sensitive to potent antimicrobial agents.

However, if the disease has been present for some time and there are fibro-caseous elements, or if any drug-resistant tubercle bacilli are present, then it appears that

specific chemotherapy will be inadequate to consolidate the good effects of adrenocortical treatment.

In all these acute cases relapse occurred when the administration of corticosteroids was reduced or stopped, if X-ray evidence of active tuberculosis was still present.

It appears that the probable mode of action of cortisone in these cases was to produce a reduction of the acute inflammatory processes and to supplement a failing, or failed, adrenal cortex. It is difficult to accept the theory that lysis of tuberculous foci occurs, thus allowing anti-tuberculosis drugs freer access to the tubercle bacilli themselves, because the blood supply to the disease areas is actually reduced, and presumably along with this the effective concentration of these drugs.

When synthesized corticosteroids were used, few obvious toxic symptoms appeared, and on the surface it seems relatively safe to continue giving them for many months. However, there is one very important factor which must influence any decision to use corticosteroid therapy—that is, atrophy of the adrenal cortex. This may be partly present before treatment with these agents is begun; but it almost always appears to develop during their administration, and is probably the reason why relapse will occur when corticosteroid therapy is stopped. The patient is just unable to muster any resistance to his disease at all.

The ideal aim of this treatment should be, therefore, to continue corticosteroid therapy *plus* effective chemotherapy until all tuberculous processes have been entirely eradicated. In this way it is hoped that there will be no tubercle bacilli left to reactivate.

Despite these complexities, it appears pertinent to suggest that if any physician intends to adhere to his obligations to "prolong life", then the withholding of corticosteroid therapy from patients dying from far-advanced tuberculosis is a neglect of his fundamental duty. It is obvious that this prolongation of life may be only delaying the end in most cases; but it also appears that the patients may thereby be given a chance to gather their reserves.

In the second group it is rather more difficult to decide whether or not to employ corticosteroids. Patients are often not desperately ill and are suffering from a self-limiting disease which makes them unable to mix in society. They have often received long-term chemotherapy, and in addition to their chronic fibro-cavitary type of disease, they may harbour some drug-resistant tubercle bacilli, even though these are not apparent by *in-vitro* methods of testing.

The aim of adrenocortical hormone treatment in this group of patients is to cause a reactivation of tuberculosis when, after a short course of therapy, these agents are withdrawn. The theory is that the blood supply to the diseased areas will thus be increased, and that previously dormant tubercle bacilli will be initiated into more rapid multiplication. If intensive chemotherapy is recommenced at that stage, then these reactivated tubercle bacilli, in previously poorly vascularized areas, will be exposed to bactericidal therapy. They will thus be killed, and the patients will be freed from their tubercle bacilli. In theory this appears to be reasonable; but unfortunately in practice this type of patient, as a result of previous inadequate chemotherapy, nearly always possesses some tubercle organisms resistant to most antituberculosis drugs. Once these resistant organisms were reactivated into multiplying again, such drugs would be incapable of controlling this process, and the disease would spread unchecked.

This may be the reason why all patients in this particular group are worse off now than before cortisone therapy was instituted, as every one showed some pre-treatment evidence of resistance to at least two of our three standard drugs. The one man who received pyrazinamide is the only one likely to maintain his present status without the further use of corticosteroids.

It appears that the withdrawal of corticosteroid therapy can cause a flare-up of chronic tuberculosis infection. Therefore, if planned treatment with these agents is con-

templated, it must be absolutely certain that there are available for use at least two specific antimicrobial drugs which can control this spread. The previous, particularly ineffective, use of any drugs such as streptomycin or INH would appear to lessen their reliability to control such a spread, and in these circumstances only a few drug-resistant organisms need continue rapid multiplication before eventually they take over the whole infected field.

In view of this, it appears justifiable to give corticosteroids to patients with chronic tuberculosis with the idea of living up their disease, only if they have not received previous streptomycin and INH therapy, or if any two other equally effective antituberculosis agents, not previously used, are available.

These criteria are unlikely to be fulfilled in this type of patient, as I consider that intensive standard chemotherapy measures should still be fully exploited in the primary treatment of tuberculosis. Pyrazinamide and cycloserine are at present unavailable, and this standard chemotherapy therefore usually includes INH and streptomycin.

Corticosteroids cannot be given for long, as adrenal cortex atrophy appears almost certain to result, and once this occurs the administration of these agents cannot be stopped. Neither can corticosteroids be given for only a short period of time, as our present chemotherapy armamentarium is not adequate to cope with an induced spread of tuberculosis caused by organisms resistant to streptomycin and INH. Thus a most unfortunate paradoxical state awaits almost every patient with chronic tuberculosis who receives this therapy.

It is recommended, therefore, that this method of treatment—adrenocortical hormone therapy *plus* chemotherapy—at present be not used for the chronic tuberculous patient, particularly if he has received previous chemotherapy.

SUMMARY.

1. The literature on adrenocortical hormone therapy in tuberculosis has been reviewed.
2. An analytical review of 12 cases of pulmonary tuberculosis treated with adrenocortical hormones *plus* chemotherapy has been presented and the implications of these findings have been discussed.
3. No clear-cut conclusions can be drawn from this small series of cases, but it appears that there is a definite place in the treatment of patients dying from far-advanced tuberculosis with adrenocortical hormones *plus* continued chemotherapy. It also appears that until a wider range of effective antituberculosis agents becomes available, adrenocortical hormone therapy should not be used in the treatment of chronic self-limiting pulmonary tuberculosis.

AN EPIDEMIC EXANTHEM ASSOCIATED WITH POLYARTHRITIS IN THE MURRAY VALLEY, 1956.¹

By S. G. ANDERSON AND E. L. FRENCH.

From the Walter and Eliza Hall Institute of Medical Research, and the Department of Experimental Medicine, University of Melbourne, Melbourne.

DURING the autumn of 1956, a widespread epidemic of mild disease was recognized by medical practitioners in towns along the Murray River from Albury in New South Wales to Walkerie in South Australia. The main features of the disease were a rash, often profuse, joint and muscle pains and a virtual absence of fever or general symptoms. In most, but not all, respects the condition resembled that described as epidemic polyarthritis during the second World War (Halliday and Horan, 1943, and others).

¹This work was done with the aid of a grant from the National Health and Medical Research Council, Canberra.

At the time of the outbreak, one of us (S.G.A.) was in Mildura on investigations concerned with the 1956 cases of Murray Valley encephalitis. The opportunity was therefore taken to carry out clinical and epidemiological studies of the condition and to obtain material for laboratory studies. A second visit was made two weeks later to allow more extensive studies to be undertaken. No evidence as to the nature of the causative agent has been obtained.

Similar investigations in South Australian towns along the Murray River are reported by Fuller and Warner (1957), and by Wilson (1957).

Clinical Picture.

Through the generous cooperation of practitioners in Mildura, 36 patients were examined with a rash in the acute stage of the disease, and the following description is based on the examination of these patients.

Prodromal Signs and Symptoms.

Symptoms and signs preceded the onset of the rash in 18 cases. In 10 cases joint and muscle pains preceded the rash by up to seven days, and one patient complained of joint pains for eleven days prior to developing a rash. In each instance the pains continued after the rash appeared. Other prodromal complaints were headache (three cases), rhinorrhoea (three cases), malaise (three cases), tenderness of palms and soles (one case), cough (one case), feverishness (one case), and adenopathy (one case).

Description of the Rash and Concurrent Symptoms and Signs.

The exanthem frequently appeared first on the cheeks, forehead and chest, and was sometimes limited to these areas. However, in the majority of cases it spread to involve all the skin surface, including scalp, palms and sometimes soles. Each lesion commenced as a pink or bright red macule two to 10 millimetres in diameter, widely separated from its fellows by skin of normal appearance. The lesions blanched on pressure. Within a day the lesions became papular in about one-third of the cases, and in an occasional case they developed the appearance of small vesicles. However, the vesicles contained very little fluid. At this stage the appearance sometimes suggested varicella, though typical ulceration and scabbing did not follow. If the rash lasted for three or four days it became darker red or dusky, but the lesions still blanched on pressure. A very occasional lesion became petechial. The duration of the rash varied from two days (12 cases) to ten days (four cases), and in one case it lasted for eighteen days. Most patients found the rash slightly itchy. In two cases the rash left a stain when it faded, and in seven cases desquamation followed.

An enanthem appeared in two cases. It consisted of a small number of dark red macules about four millimetres in diameter on the hard and soft palates. These lesions did not blanch on pressure.

Only one patient complained of what might have been an eschar. It had appeared about a week before the rash, was situated on the forehead, was about half an inch in diameter, but was not grossly necrotic. In our opinion it did not represent an eschar. Eighteen other patients were carefully examined for an eschar, within two days of onset of the rash. None was found.

Of the 35 patients, 23 complained of joint or muscle pains; the joints most commonly involved were the metacarpo-phalangeal and interphalangeal joints, but larger joints were also affected occasionally. There was often transient limitation of movement, but swelling of the joints was rare. One patient developed effusion into both knee joints. These joint pains lasted from two to twenty-eight days, but in most cases had cleared by fourteen days.

The temperature was recorded in 12 cases on the first day of the rash. In nine cases the temperature was normal and in three cases elevated (99°, 100.5° and 100.8° F. respectively). Of the other 24 patients, only two gave a history of feeling feverish at the beginning of the rash.

Moderately painful enlargement of glands was noted in five cases; three patients exhibited post-auricular adenopathy, and in four cases glands in the anterior cervical triangles or axillae or groins were enlarged.

Headache (11 cases) was mild and transient. Retro-orbital pain, as distinct from frontal headache, occurred in only one case on the day of onset of the rash and persisted for forty-eight hours. The eyeballs were not tender.

Sore throat was present in one case at the onset, and mild pharyngeal catarrh was noted by several other patients. Neither of the two patients with an enanthem admitted to soreness of the throat or palate. Anorexia and nausea (two cases) were mild. Tenderness of palms or soles was present in five cases at the onset of the rash, and in one case on the day before the rash. Paresthesiae (five cases) included numbness and tingling of the fingers and toes. When present, this was a most dramatic symptom.

White blood cells were examined both at the Mildura Base Hospital and at the Royal Melbourne Hospital. The total leucocyte counts ranged from 2800 to 7000 per cubic millimetre, and differential counts, estimated by Dr. D. C. Cowling, of the Royal Melbourne Hospital, were within normal limits.

There were no perversions of taste or psychiatric symptoms. Neither conjunctivitis nor photophobia occurred. Bowel and bladder function was not affected. There was no instance of clinical relapse, but joint pains persisted in some cases for at least eight months.

Many other patients complained of joint and muscle pains without a rash. These probably suffered from the same disease, but there appeared to be no way to confirm this.

Epidemiology.

Although we have described only 36 cases, 20 in male and 16 in female subjects, the epidemic in Mildura, with a population of about 20,000, is estimated to have provided between 1000 and 2000 cases of the disease between April 1 and May 17, 1956. In the 36 cases described, all the infections were received within 20 miles of Mildura in north-west Victoria. Medical officers between Mildura and Albury reported that cases of the disease occurred in Robinvale, Balranald on the Murrumbidgee River, Nyah West, Swan Hill, Corowa and Albury (Figure 1). The majority of Victorian cases probably occurred in Mildura and Robinvale.

Medical practitioners in Sea Lake, Ouyen, Manangatang and Shepparton stated that they had seen no cases among their local population, with the exception of several persons who had visited the Murray River during the preceding few weeks. No similar disease was reported from other country towns in Victoria, and it is thought that within Victoria this disease was acquired only in the Murray Valley. In view of this, further questions were asked of 27 of the Mildura patients. All had been in close association with the river between one and two weeks before the onset of the rash—for example, picnicking or gathering wood along the river banks, or fishing or boating on the river or its backwaters. This finding is probably significant, although many residents of Mildura normally spend their leisure by the river.

Among the 36 cases described above, only three patients had been in homes where another case of the disease had appeared. In one instance, a man, aged twenty-eight years, told of his wife, who had developed a rash and joint pains on the same day as he. The second patient was a boy, aged twenty months, whose brother, aged three months, had developed an exanthem two days previously. Three adults in this household remained free of symptoms. The third patient, a man, aged fifty years, had nursed a child with "measles" twelve days before. In view of the great number of cases in Mildura at this time, it seems that this latter instance may be fortuitous. One patient contracted the disease a few days after he left Mildura for an army camp in southern Victoria. On the initiative of Dr. J. Bunday, of Mildura, and through the courtesy of the Deputy Director of Medical Services, Southern Command, Colonel J. Glyn-White, a questionnaire was sent

to every camp contact of the patient. Dr. Bundey reports that "almost every copy of the questionnaire was returned and all answers were negative". That is, there was no report of a camp contact developing a similar rash. We believe that there was suggestive evidence that this disease was not infectious by personal contact.

Through the generous cooperation of the Minister of Health for Victoria, and the Chairman of the Health Commission, a request was made in the Melbourne newspapers for people suspected of having had the rash in question to get into touch with this institute. We were somewhat overwhelmed by the large number of persons who reported—156 in all. Each had developed a rash after leaving the Murray Valley in north-western Victoria.

A careful assessment was made of the clinical condition, without regard to the interval elapsing between departure from the valley and development of the rash. In 14 of these cases we were satisfied that the disease described by the patient or his physician was the rash in question. All these persons gave a history of close contact with the Murray River.

The possible incubation periods of the disease in these 14 cases were calculated on the assumption that the infection was acquired in the Murray Valley. They were, in days, as follows: 0 to 15, 2 to 15, 5 to 10, 6 to 15, 7 to 12, 7 to 12, 7 to 16, 8 to 16, 8 to 18, 9 to 23, 10 to 15, 10 to 17, 11 to 16, 28 to 31. If the last figure of 28 to 31 is excluded, an incubation period of 10 to 11 days would fit all cases. It is possible that the incubation period varied considerably between patients, and the figure for the last case (28 to 31 days) might support this idea of a variable incubation period.

Attempts to Identify an Infective Agent.

Attempts were made on two occasions to isolate an infective agent from typical cases of this disease. At the first attempt specimens of heparinized blood from six patients were forwarded to Melbourne from Mildura in sealed ampoules at about -70°C , on dry ice. This material was inoculated intraperitoneally into adult mice and into the yolk sac of chick embryos. The mice remained well over a period of six weeks, and no microorganism was isolated from the chick embryos despite blind passage of the yolk-sac and embryo tissue.

The second attempt at isolation was made by taking chick embryos, mice, guinea-pigs and tissue cultures to Mildura and making on the spot the inoculations of material from patients in the acute stages of the rash. Specimens of blood, throat washings, urine and skin scrapings from four patients with the typical disease were collected within twenty-four hours of onset and used for inoculation in this way. The blood, skin scrapings and throat washings were inoculated in suckling mice less than forty-eight hours old, some by the peritoneal route and some by the intracerebral route. Adult mice were also inoculated intraperitoneally and intracerebrally with the same material. The guinea-pigs were inoculated intraperitoneally with blood, throat washings, skin scrapings and urine. Tissue cultures of trypsinized human amnion cells and porcine kidney cells were inoculated with blood,

throat washings and skin scrapings. Chick embryos were inoculated with blood by the yolk sac and with blood and throat washings on the chorio-allantoic membrane. Blind passages of all these cultures were carried out at appropriate intervals, and passage material was inoculated into Fletcher's medium for leptospiræ. No evidence was obtained of the growth of any microorganism.

About 30 paired sera—that is, acute phase and two to four weeks convalescent specimens—were submitted to agglutination tests with the three Proteus antigens OXK, OX19 and OX2. None of these showed a significant rise in titre against any of the bacterial suspensions.

In the course of a search for Murray Valley encephalitis virus in 1952, seven viruses were isolated from pools of mosquitoes caught in the Mildura area. Five of these viruses were shown to be related to fowl pox virus, and they probably represented strains of bird pox viruses

prevalent in the area at the time. The other two viruses differed from the pox viruses in producing very small lesions on the chorio-allantoic membrane of chick embryos, and they were not neutralized by anti-sera prepared against the pox viruses or the virus of infectious laryngotracheitis (French and Reeves, 1954). In addition, an unidentified virus producing pocks on the chorio-allantoic membrane of chick embryos was isolated from the blood of a nestling cormorant (French, 1954). In the absence of any demonstrated aetiology of the rash, it

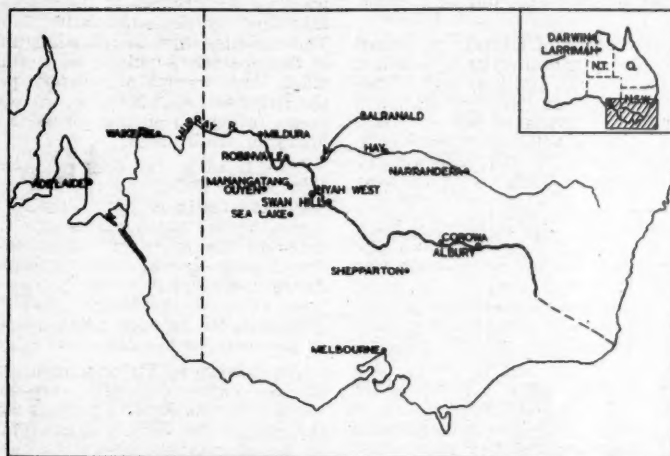


FIGURE 1.

was decided to examine representative sera for antibody to these viruses, although there was no indication that they caused the disease.

Acute and convalescent phase sera from 10 patients who had suffered from the rash were put up with suitable dilutions of one of the bird-pox viruses (CA 1), one of the small pox-producing viruses (CF 5) and the cormorant virus (LVC) in neutralization tests on the chorio-allantoic membrane. None of the sera caused any significant neutralization of these viruses. The significance of results with CF 5 and LVC is doubtful, as neutralization of these viruses on the chorio-allantoic membrane had not been demonstrated with serum from human or "immunized" laboratory animals (French and Reeves, 1954).

Possible Vectors of the Disease.

In the absence of information about the aetiological agent of the disease, it is difficult to form any opinion on possible vectors or reservoirs of the agent. Mr. G. Douglas, of the Commonwealth Scientific and Industrial Research Organization, stated that the normal autumn prevalence of mosquitoes was seen during 1956, that sandflies (*Phlebotomus* species) are always present, and that this year was no exception. There was a notable increase in the density of wild mice around Mildura and in the desert to the south of Mildura, but this increase had by no means reached plague proportions. The preceding summer had been exceptionally wet, and there was considerable flooding of riverside areas right along the Murray River at the time of the outbreak of the rash.

Particularly in view of earlier reports of "biting flies" being associated with epidemic polyarthritis, it is of some

interest that March flies (*Tabanidae*) were prevalent and troublesome to humans in the Murray Valley, just before and during the period of the epidemic.

Summary of Relevant Literature.

Nimmo (1928a, b) gives a brief description of an epidemic in Narrandera during March and April, 1928; the description could fit the current 1956 rash. He mentions the prevalence of *Culex* mosquitoes and "stinging flies". The epidemic involved at least 100 persons near Narrandera, affecting mostly country dwellers rather than town dwellers.

Edwards (1928) briefly reports the same type of epidemic in Hay, starting about six weeks before the Narrandera epidemic. Edwards considers the disease an atypical form of dengue, but could find no *Stegomyia fasciata* (*Aedes aegypti*). In a later letter, Nimmo (1946) comments that in south-western New South Wales 1928 was an abnormally wet season. He states that some years after 1928 he saw the same disease in the Torres Strait area during the wet season.

During the war, when large groups of military personnel were stationed in northern Australia, outbreaks of epidemic polyarthritis occurred in the troops. Halliday and Horan (1943) first described the disease in soldiers stationed between Darwin, Larrimah and Adelaide River. One hundred and five cases were seen between November 1, 1942, and January 31, 1943, and there had been similar cases in the few months preceding November, 1942. Culicine mosquitoes were present.

In the same general area, but, fifteen months later, Goswell (1946) reported 51 cases occurring within the space of ten days. He stated that the site of infection was about 300 miles south of Darwin. Despite the close quartering of troops, there was a notable absence of person-to-person infection. No ticks, mites or sandflies were present. There were a few mosquitoes, mainly culicine, in the area; but Goswell emphasized the fact that three weeks before the outbreak, March flies had become very prevalent and had bitten the troops extensively.

Harris (1944) observed 40 cases, mostly within 30 miles of Adelaide River, during November and December, 1943, and a further 25 cases before April 1, 1944.

Sibree (1944) observed 28 cases during late February and early March, 1944, in a military camp in Queensland. Culicine mosquitoes were abundant at the time. Sibree quoted C. H. Knott as stating that during 1940 there had been an epidemic in the same area amongst civilians; it had been generally considered to be rubella, but in some cases the disease was followed by persistent joint pains.

Dowling (1946) described 94 cases among troops in North Queensland during February, March and April, 1945. He commented that that year was the third successive year during which such an epidemic had occurred in troops in northern Australia during the normal "wet" season. The outbreak he described began "about two weeks after heavy falls of rain had converted into swamps much of the area in the neighbourhood of the . . . 86 cases". At the same time, mosquitoes had become much more numerous. They were various species of culicines, and in two of the five camps involved, *Anopheles annulipes* was found.

Discussion.

In the absence of positive aetiological findings, discussion must be confined to clinical and epidemiological aspects.

The clinical features of this exanthem were not typical of any of the common infectious diseases. However, they closely resembled the descriptions of epidemic polyarthritis published during the war by Halliday and Horan (1943) and others.

Dr. J. P. Horan kindly consented to examine colour photographs of a number of patients affected during 1956. His opinion was that the present outbreak could have been the same disease as that which he and Halliday had studied in 1942-1943; but he stressed that their patients had no lesions on either the face or the palate, and that the individual lesions in the case in the Northern Territory had been more widely separated than in the Mildura cases.

These may be minor differences. Indeed, even in the descriptions published by various authors during the war, there are similar slight variations in clinical description—notably regarding the incidence of lymph-gland enlargement. We therefore tentatively assume that the rash described in this communication is identical with the wartime epidemics of polyarthritis. Because of the (admittedly brief) clinical description, and because of the situation and time of the outbreak in 1928 in Narrandera and Hay, we are inclined to accept that also as the same disease.

There are thus records of six epidemics of polyarthritis. During the war it occurred in troops in the Darwin-Adelaide River-Larrimah area of the Northern Territory during the wet seasons of 1942-1943 and 1943-1944, and during the wet seasons in Queensland during early 1944 and early 1945. It probably extended to the south and east during February, March and April, 1928, and came south again during April and May, 1956. The sites of wartime occurrences of the disease are normally sparsely inhabited by nomadic natives and a few white settlers. The situation then suggests an infectious agent, persisting in this sparsely populated area, and flaring into prominence when large groups of military personnel are moved into the endemic area. Even so, the appearance of an epidemic seems to depend on the normal seasonal rainfall, which is heavy in those areas.

On this basis, the occurrence of the disease in western New South Wales and the Murray Valley of Victoria and South Australia might be due to the occasional spread of the infectious agent southwards from its more permanent home in the north of Australia. An analogy might be drawn with Murray Valley encephalitis (Anderson, 1954). Another possibility would be the persistence of the infectious agent in the Murray Valley as well as in northern Australia, but in such a manner as to infect humans only occasionally in the Murray Valley.

The disease in Victoria apparently occurred only in the Murray Valley. Detailed investigations suggest that it was strictly confined to persons who had close contact with the river. The local rainfall and flooding were excessive in the Murray Valley during the 1955-1956 summer, and this may be a major factor in precipitating the rare outbreaks in the Murray Valley.

In this discussion we have assumed that the disease is infectious. That was also the opinion of all but one of the previous authors. Facts which suggest an infectious agent in the present outbreak are the clinical picture, the high incidence in the population of Mildura (5% to 10%), the incubation period of about ten days, the occasional and seasonal incidence, and the close association with the river.

The two last-mentioned facts, together with the absence of case-to-case infection, would be consistent with an infectious agent transmitted by arthropods from non-human vertebrate hosts, either or both vector and host being closely restricted to the river or flood waters.

The observed facts might also be consistent with the presence of an infectious agent in river and flood water, although we are not aware of any leptospira or schistosome which produces this clinical and epidemiological picture. Kelly (1943) has suggested a relation between the Australian disease and rat-bite fever.

It is probable that further outbreaks of this disease will occur in Australia from time to time, particularly as human populations increase in the north of the continent. Attempts to isolate the aetiological agent are still called for, and two approaches may be suggested if future opportunities arise. These are to intensify efforts to grow leptospira in culture from blood and urine in early cases, and to test the possibility of transmitting the condition to human volunteers living outside the endemic area, by means of culicine or anopheline mosquitoes or *Tabanidae* which had fed on human subjects in the acute stage.

Summary.

During April and May, 1956, a mild epidemic disease appeared along the Murray River in northern Victoria and

South Australia. The predominant clinical features were a maculo-papular rash and joint and muscle pains.

It is estimated that between 5% and 10% of the population of Mildura was affected. Thirty-six cases were studied in detail.

No infectious agent could be isolated.

The disease may be a recurrence of that described by Halliday and Horan as "epidemic polyarthrititis".

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SOME EPIDEMIOLOGICAL AND LABORATORY OBSERVATIONS ON AN EPIDEMIC RASH AND POLYARTHRITIS OCCURRING IN THE UPPER MURRAY REGION OF SOUTH AUSTRALIA.

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In April, 1956, shortly after Easter, an outbreak of a disease occurred in the Murray Valley mainly in the area lying between Mildura and Walkerie. The disease was usually very mild, its most prominent feature being the presence of a maculo-papular rash, usually of short duration, accompanied not infrequently by polyarthrititis.

Our attention was drawn to the epidemic in early May, whereupon we visited the affected area in South Australia.

We discussed the disease with the local medical practitioners who were kind enough to allow us to interview and obtain specimens of blood from some of their patients. Subsequently a questionnaire was sent to the practitioners in the State to determine the geographical limits of the epidemic.

Our purpose in carrying out this investigation was to identify the disease, to attempt to isolate an aetiological agent and to determine its epidemiological features. Anderson and French (1957) and Wilson (1957) are presenting clinical studies of the epidemic. Although we carried out no detailed clinical survey beyond that sufficient to identify the disease, we thought it worth while to record the results of our inquiry in an attempt to complete the picture of what is probably an uncommon malady.

It appeared, from discussions with practitioners, that the most characteristic feature of the disease was a maculo-papular rash of short duration. The rash was not necessarily widely distributed over the body in individual patients, but no part of the skin was exempt. It was generally maculo-papular, not usually itchy, and faded within a few days. Joint pains occurred not infrequently. These affected, sometimes with swelling, one or more joints of the limbs and extremities and only rarely the hips and shoulders. Joint pains persisted for longer than the rash, but decreased gradually, with complete recovery usually within four weeks. Malaise and miscellaneous minor symptoms, such as mild headache and backache, were inconstant features. Pyrexia was slight or absent. Unusual features were the occasional complaints of drowsiness or "pins and needles". The onset of the disease was variable; usually either joint or limb pain or rash was first noticed, but occasionally malaise was the presenting feature. The course of the disease was usually mild; in some cases joint pains and in others the rash were absent. Only a small proportion of sufferers, being disabled by joint or limb pain, retired to bed. No sequelae have been recorded. It is estimated that approximately 200 cases were drawn to the attention of practitioners in the Upper Murray district of South Australia. Most of these occurred in the Berri-Barmera-Renmark area. The first cases were recognized shortly after Easter, and the main outbreak occurred in the month of April and diminished throughout May and early June, when it disappeared.

Clinical Features.

We visited the Upper Murray district in South Australia at the beginning of May, when the epidemic was declining. We interviewed 16 patients resident in the district, and in many instances obtained confirmation of their observations from their doctors. The main clinical features are shown in Table I. Three patients (Cases IX, X and XIII) were seen in the acute stage with rash, at intervals of one, two and five days respectively after the onset. One patient (Case XI), whose rash was fading, was seen on the sixteenth day after the onset. Six patients (Cases II, XII, XIV, XV, XVI and XVII) still had joint pains seven to thirty days after the onset. Six patients (Cases I, III, IV, V, VII and VIII) had completely recovered, and were seen from between thirteen and thirty days after the onset. The rash occurred in 15 out of 16 of the patients. It was maculo-papular in all but one (Case VIII), who described it as blotchy. The rash most commonly occurred on the arms, legs and face; but there was no part of the body that was not involved in one or other of the patients. It usually started in one place and then spread to others. It lasted from one to sixteen days, with an average of three to four days. The rash was the presenting symptom in seven cases (or perhaps eight, if we include Case XI; this patient stated that a red nose was the first sign). Two patients noticed malaise or other minor disturbances at the time of the appearance of the rash. The joints involved were nearly always those of the limbs, and sometimes pain was noticed in other parts of the limbs. Two patients complained of shoulder pain and one of pain in the back of the neck. The joint pains persisted for longer than the rash; in two patients they had not disappeared after twenty-eight days, and in one after thirty days.

TABLE I.

Case Number.	Rash.			Joint and Limb Pains.			Presenting Symptoms.		Total Duration. (Days.)
	Day of Onset.	Distribution.	Duration. (Days.)	Day of Onset.	Site.	Duration. (Days.)	Type.	Duration. (Days.)	
I ¹	3	Arms and legs.	1 or 1.5	1	Hands and feet.	10 to 14	Headache. Drowsiness. Joint pains.	2 10 to 14	10 to 14.
II	2	First on face, then extremities.	3	1 2	Left forearm, fingers. Knees.	7	Joint pains.	7	Still joint pains at 7 days.
III ¹	1	First on face, then arms and legs.	2	Few days after rash.	Fingers, hands.	—	Rash. Drowsiness.	2 2 or 3	About 14 days.
IV	5	First hands, then body and face.	3	5	Hands, right arm. Fingers, toes.	30	Joints.	30	30
V	1	First on face, arms and legs, then trunk.	5	After rash.	Knees, shoulders.	About 5 days.	Rash.	5	About 5 days.
VII	3 or 4	Legs.	2 or 3	1	Shoulder, ankles, soles of feet.	21	Joint pains.	21	21
VIII ²	1	Face, trunk, arms.	1.5	Nil.	Nil.	Nil.	Headache. Vomiting. Rash. Backache. Drowsiness.	1.5	About 2.
IX ¹	1	First left arm, then face, legs, right arm and body.	—	—	—	—	—	—	Seen on first day of disease.
X	1 2	Right arm, shoulder and hand. Legs.	Fading at 5 days.	—	—	—	Rash.	5	Seen on fifth day of disease.
XI ³	4	First face, then all over body.	Almost faded at 16 days.	5	Wrists, knees.	Some pain at 16 days.	Red nose.	—	Seen on sixteenth day of disease.
XII	"After joints."	Legs and arms.	1	1 4	Left knee. Right wrist.	28	Joints.	28	In bed 3 weeks "not fit" after 28 days.
XIII	1	Face, body, legs and scalp.	2	—	—	—	Rash.	2	Seen on second day of illness.
XIV	Nil.	Nil.	Nil.	1	Knees. Wrists, back of neck.	2 or 3 Later.	Joints.	30	Some pain in wrists persists after 30 days.
XV	Few days after joints.	Legs and arms.	7	1	Knees, hands.	15	Joints.	15	Hands still very stiff after 15 days.
XVI	1	First feet, ankles, then forearms.	4 or 5	"Before rash faded."	Knees, ankles, hands, right arm.	28	Rash.	4-5	Left hand and right arm still painful after 28 days.
XVII	1	First legs, then body and face.	8 or 9	"After rash."	Feet, ankles.	12	Rash.	8-9	Ankles still painful after 12 days.

¹ Complained of pins and needles.² This patient complained of a "blotchy reddish" rash only.³ This patient had a few petechiae.

Two patients complained of having suffered from drowsiness and "pins and needles". One patient (Case VIII) complained of drowsiness associated with vomiting, backache and headache. There is some doubt whether this patient should be included here, as her rash was atypical and she did not have joint pains. If she is excluded, then every patient seen by us suffered from joint pains. However, it is known that joint pains were not invariably present, and the patients we examined cannot be regarded as a random sample.

Epidemiological Features.

The above-mentioned patients and the local medical practitioners were questioned about possible epidemiological factors, such as contacts, number of cases in the household, the type of sewage, drinking water, milk and meat supplies, proximity to the river, social activities and contact with possible allergens.

There was no evidence that the disease was more prevalent in either sex. However, it seemed uncommon among children. There was no evidence of person-to-person infection. Only one case occurred in a household where there was another doubtful case; but, since the family included 19 children, this was not thought significant.

Everyone agreed upon the facts that there had been a particularly rainy season (Wilson, 1957), and that there were more mosquitoes than usual. The other fact which emerged, and which may be significant, is that at Easter a regatta was held on Lake Bonney at Barmera, at which several thousands of people were estimated to have been present. Such a gathering could plausibly account for a sudden outbreak of a disease possessing the clinical features described above, and would support a hypothesis that the causal agent was a virus transmitted by mosquitoes.

On May 28, 1956, a questionnaire was sent to all the practitioners in South Australia. The disease was briefly described, and the following information was requested: (i) the number of patients with the condition in the area; (ii) the date of occurrence of the illness in each case; (iii) the location of each patient; (iv) whether the patient had any contact with the River Murray district; (v) if so, when and where; (vi) whether there were excessive numbers of mice and mosquitoes.

Nine replies were received describing 11 instances of a disease resembling our description which occurred between April 8 and May 31. From the descriptions, seven of the patients appeared to have suffered from typical attacks. Of these, five had visited the Murray Valley region for brief periods preceding their attacks, but normally resided at a distance from it. On the assumption that these people had been infected in the Murray Valley region, it was possible to calculate the ranges for the incubation period for all. These were as follows: eight to twelve, fifteen, six to ten, four to six and three to eleven days. Thus it would be possible to state that the incubation period can certainly be as short as six and as long as fifteen days, and that it may have been as short as three days. Two apparently typical cases occurred in people who had not visited the Murray area at all.

One of these, a married woman, had been presented with a large quantity of sultanas from Renmark on April 2. She left them to dry until May 21, when she stemmed them, kneeling in them for some time to do so. Two days later a rash started on the thighs, and the subsequent history suggested that her illness was a typical example of the disease we have described.

Of four patients whose disease did not seem to fit that under discussion, none had contact with the Murray region, although one lived within 20 miles of it.

Thus, of seven patients whose disease conformed to that we have described, five had visited the Murray region, whereas only two from the whole of the State occurred among people who had not.

Laboratory Investigations.

Specimens of whole blood were obtained from 14 of the patients we saw (Cases I, III, IV, V, VI, VII, IX, XI, XII, XIII, XIV, XV, XVI and XVII). All specimens reached the laboratory within thirty-six hours, where they were refrigerated. Clots and serum were separated within forty-eight hours.

Attempt at Virus Isolation.

Specimens of blood clot from five patients, including two in the acute stage (Cases IX and XIII), taken on the first and second days of the disease, and from three (Cases XI, XII and XV) with residual joint pains, were examined separately. The remaining nine specimens of blood clots were pooled to form one specimen. The specimens were ground with sand in a mortar, and approximately one to three times the amount of 10% rabbit serum saline was added. The mixtures were allowed to stand and the supernatant was used for inoculation. Each of the six specimens was inoculated intraperitoneally into two guinea-pigs and into mice, some being inoculated intraperitoneally and some intracerebrally. The yolk sacs of embryonated eggs (six day) were inoculated also. The guinea-pigs showed no illness or elevation of temperature, which was taken daily for fifteen days. Some mice showed signs of illness which were attributable to other causes; however, the blood from the patients in the acute stages and the pooled specimens went through from three to five serial passages without the detection of an infectious agent. No deaths occurred among the embryonated eggs.

Serological Tests.

Agglutination tests for the following antigens were carried out on 14 sera: *Salmonella typhi* H, *S. typhi* O, *S. paratyphi* A H, *S. paratyphi* B sp. H, *S. paratyphi* B O, *Proteus* OX19. All the results were negative.

The following results were obtained to the complement-fixation test: (i) psittacosis, 12 sera, four positive results (low titre), eight negative results; (ii) "Q" fever, 13 sera, all results negative; (iii) Murray Valley encephalitis, 13 sera, one positive result (one in five); (iv) murine typhus, 13 sera, all results negative.

Discussion.

From our inquiries, it was plain that the epidemic in the Upper Murray region of South Australia was an outbreak of a well-defined disease characterized by its mildness, a rash of short duration and the frequent occurrence of polyarthritides. Also it was obvious that it was the same disease as that occurring in the contiguous region of Victoria (Anderson and French, 1957).

It seems certain that the epidemic was confined to the Murray Valley. This was shown by the fact that, in response to our questionnaire, only seven reports of a similar illness were received from other parts of the State, and of these patients, five had visited the epidemic area less than fifteen days before their illness. Three of them visited the region at Easter. These features, together with the fact that there was no evidence of person-to-person spread, are suggestive of an infectious disease carried by insects, which were known to be numerous.

As epidemics have not been reported in previous years, it is unlikely that the infectious agent is normally carried by mosquitoes, and it is necessary to postulate an animal or avian reservoir. The suddenness of the outbreak, followed by its more gradual disappearance, suggests (i) that the infectious agent is not normally present in the region, or (ii) that, if it is, its presence was revealed by a concentration of large numbers of susceptible human beings, or (iii) that both these factors may have played a part. If this is borne in mind, it is significant that the first cases were recognized a few days after the Easter holiday, when a regatta on Lake Bonney was attended by several thousands of people from all the towns (Victorian and South Australian) in the region involved by the epidemic. If, as we have suggested, the disease was caused by a virus carried by insects, then it is possible to assign to it an incubation period of somewhere between three and fifteen days, from the information given by those sufferers who had visited the epidemic region for known short periods.

Another explanation of the disease, suggested by at least one local practitioner and contributed to by a number of those suffering from it, was that it was an allergic reaction to moulds, which at this time were attacking grapes on the vine. This may appear to be supported by the occurrence of what seems to have been the typical disease in a woman whose only contact with the Murray Valley was that she had knelt in sultanas from there two days before she developed the rash on her thighs. However, the disease occurred among many who had never had contact with grapes. Also the length of the incubation period does not suggest an allergic phenomenon.

While we were attempting to discover accounts of similar outbreaks, our attention was drawn by Dr. K. V. Sanderson, of the Institute of Medical and Veterinary Science, Adelaide, to the publications of Halliday and Horan (1943), of Sibree (1944) and of Dowling (1946). These authors describe outbreaks of epidemic polyarthritides, usually accompanied by a rash, occurring in military units in the Northern Territory. The features of the disease they describe accord very nearly with those described here. One notable difference is that all three give greater prominence to the occurrence of polyarthritides, whereas in the present epidemic the rash was the most notable feature. This difference may merely be the result of the contrasting conditions in military and civilian life. Halliday and Horan (1943) state that the face was always spared by the rash, that mild fever and tender adenitis were almost invariable. However, both Sibree (1944) and Dowling (1946) found that the whole skin surface could be involved by the rash, and that neither fever nor adenitis was invariably present. Both Sibree (1944) and Dowling (1946) conclude that the outbreaks they discovered were of the disease described by Halliday and Horan (1943). One interesting feature is that Dowling (1946) comments on the occurrence of "pins and needles", as did two of the sixteen patients seen by us. The three publications discuss the differential diagnosis, and agree that the disease is distinct from dengue, rheumatic fever, rheumatoid arthritis, rubella, varicella, glandular fever and meningococcal infection.

Certain epidemiological features of all four outbreaks are similar. They occurred during a period of two to three months among a fairly closely grouped population in wet seasons when mosquitoes were prevalent. Thus there seems very little doubt that the disease which occurred in the Murray Valley in 1956 was the same as, or closely related to, that which occurred in Queensland and the Northern Territory in 1942-1943, 1944 and 1945.

Weston Hurst (see Halliday and Horan, 1943) and Anderson and French (1957) failed to isolate an infectious agent. We have also isolated no virus or rickettsial agent, and serological examinations for common bacterial and viral antibodies have revealed nothing. However, on the whole it seems reasonable to assume that this and previous epidemics had a common or closely related causal agent—namely, a virus—spread by an insect vector. Its occasional appearance in human beings suggests an animal reservoir, the infectivity of which is either low or variable, and which is from time to time revealed by an unusual concentration of human beings.

To speculate further, an interesting parallel can be drawn between this pattern of epidemiological behaviour and that of Murray Valley encephalitis, itself an infrequent visitor to the same region and, in all probability, transmitted by mosquitoes from an avian reservoir. Just as the Murray Valley encephalitis virus may normally be resident in the northern parts of Australia, so may the agent of the disease we have described, its presence being revealed by the introduction of groups of susceptible soldiers.

The apparent rarity of the disease and the failure to isolate an aetiological agent hamper further investigation. Another approach is to isolate, from suspected vectors or reservoirs, viruses such as those obtained from mosquitoes by French and Reeves (1954). These could be tested against convalescent sera from patients who had suffered from the disease. In this connexion it would be important to encourage the recognition of the disease and the safe-keeping of convalescent sera from sufferers.

Summary.

The occurrence is recorded of an epidemic disease, characterized by a rash and polyarthritides, in the Upper Murray region of South Australia. The results of interviews with 16 patients, the failure to identify an infectious agent with the blood of 14 and the epidemiological features are described. The present epidemic is compared with three previous epidemics in the Northern Territory and Queensland. It is concluded that all four epidemics were caused by the same or a closely related infectious agent spread by mosquitoes from an animal reservoir. It is thought that the epidemic in the Murray region may have been initiated by the unusual concentration of susceptible people attending a regatta on Lake Bonney during Easter, 1956.

Acknowledgements.

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THE MURRAY VALLEY RASH.

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IN April, 1956, there occurred at Renmark, South Australia, an epidemic of an illness whose chief feature was a characteristic rash. Only 45 cases have been recorded here, and certain general features and conclusions have been arrived at, perhaps on far too small a number. As the illness did not incapacitate most of the patients, and as it became generally known that the disease was in the area and was harmless, very many did not report. It is therefore certain that many more cases occurred, and I heard of these cases from patients and formed the impression that the illness was widespread. The outbreak occurred between April 9 and May 19, 1956, no new cases being seen before or after these dates in the area.

Clinical Features.

The Rash.

The rash, as mentioned, was the main feature of the illness. In most cases it was a maculo-papular eruption, the lesions being often discrete and red, and pin-point in size. In others the coalescence of the lesions gave the rash a more blotchy, often decidedly morbilliform character. In fact, many of the patients diagnosed their illness as rubella, and often the rash appeared very similar. In yet other cases the rash was raised, owing to considerable intradermal oedema, and appeared urticarial in type. This was seen especially around the face and neck. In other cases again the rash was vesicular, and rarely was it petechial in nature. On the whole, however, the lesions were small and raised, and could often be felt rather than seen in the early stages. The lesions often first occurred on the wrists and ankles, and some irritability in the shirt-sleeve or sock area would bring the rash to the person's notice. There seemed no predilection for the palmar aspect of the wrists, as is often seen in contact dermatitis, and the rash often occurred on the palms and soles themselves, so that the appearances suggested a systemic origin. The rash often quickly became generalized in the more severe cases, and was often most intense on the face and neck. All degrees of severity of the rash occurred, and a wide range of variations were seen; but in general the rash ran true to type.

It was a feature of the rash that it developed rapidly in all sites. Almost from the first appearance of the rash, it quickly reached its peak in a few hours, and one could feel confident that the rash would not spread or reappear after one had first examined the patient. In some cases the rash disappeared overnight, but in most it lasted for two or three days, before slowly fading. In some of the more severe cases it lasted for a week to ten days, and on fading left behind a characteristic copper staining, as seen in roseola. As far as irritability of the rash is concerned, out of the 45 cases there were 15 in which the itching was intense, 16 in which it was only slight, and 14 in which no irritation was recorded; that is, in roughly one-third of the cases there was no irritability at all. Those cases in which the rash was extremely irritating were usually those in which it was widespread, often all over the face, and in which it had a more urticarial appearance than the usual pin-point, slightly irritating lesion.

Other Clinical Features.

The general symptoms of the condition varied a great deal. In most cases there was very little constitutional disturbance other than a slight feeling of vague malaise. In others, there was the complaint of a slight headache, some fever and general vague muscle pains; other patients began their illness with influenza-like symptoms. Some patients even declared themselves perfectly fit. In fact, it was this common feature of lack of general symptoms combined with a widespread rash that was the most outstanding feature of the illness.

Slightly more than one-third of the patients in the series complained of joint pains. This figure is possibly on the low side, as unless the symptom was specifically asked for, many patients would not volunteer the information, as the pain or stiffness was often only mild. A joint commonly found to be involved was the metacarpo-phalangeal joint of the index finger, and often on being asked about joint symptoms, the patient would point here. In only one case (Case 3) were the pain and swelling of the joints severe enough to incapacitate the patient. This case occurred early in the series and reminded me of so-called serum sickness. In this case, all joints were involved, especially the knees and ankles. The joints were painful, swollen, hot and tender, with considerable periarticular swelling especially of the knees. This patient therefore presented with polyarthritis and the rash, and took two weeks before he was up and about again. The usual joint features were slight periarticular swelling and some stiffness only, often not of sufficient magnitude to warrant special mention.

Lymph-gland enlargement was not a constant feature of the outbreak. The axillary and inguinal glands were enlarged in roughly one-quarter of the cases, in some quite prominently so. There seemed no special features about these cases, other than the fact that the more severe the case with perhaps joint symptoms, the more likelihood was there of finding lymphadenopathy. The occipital glands were noticed in several cases, and this, with the rash and general malaise, reminded one of rubella. Had it not been for the epidemic, an isolated case might have been diagnosed as rubella.

In connexion with the reticulo-endothelial system, in only one case (Case 31) was the spleen palpable. This patient had a widespread rash, felt ill, and had enlarged lymph glands and no joint symptoms. He recovered rapidly, as was the rule, and the enlargement of his glands and spleen quickly subsided.

The presence of small vesicles on the soft palate was seen in only two cases. This fact has no special significance, other than the fact that it is commonly seen in virus infections. Thus an aetiology along these lines is suggested in these cases.

In all except five cases, the rash had disappeared in two to three days, and the person was well. In these five cases either the rash or the joint symptoms were severe, and even these patients made a complete recovery inside two weeks. No sequelae or relapses were seen. Several blood examinations, including haemoglobin estimation and leucocyte and differential leucocyte counts, were performed, and all gave normal results; so the investigation was not continued in all cases.

In no case was there clinical evidence of lung disease, but owing to the possibility that the illness might be "Q" fever, several chest X-ray examinations were performed, but revealed no abnormality. The ancillary aids, therefore, were not of any help in diagnosis, and I depended solely on the clinical features. Some blood samples were kindly collected by Dr. P. Warner, from the Institute of Medical and Veterinary Science, Adelaide, but so far no causative organism has been isolated (Fuller and Warner, 1957).

Summary of Findings from the Outbreak.

From the study of the cases, there was a definite preponderance of male patients in the proportion of 2:1. Most cases occurred in the young to middle-age group. Only four cases occurred in children aged under twelve years, and no affected infant was seen. Of course, at this age it would be very difficult to diagnose, especially from *roseola infantum*. The incubation period has been estimated at about fourteen days. It is certainly less than three weeks, as is seen by Case 40, in which the patient entered the district from another State three weeks prior to the onset of the rash. There was one week between the onsets of the rash in Cases 24 and 25 (husband and wife), in which direct personal contact is likely; also the husband (Case 24) maintained that he had acquired his rash fourteen

days after the patient in Case 10—they both worked at the same fruit-packing shed together. In many cases not recorded here, the patients, on being questioned, could remember a contact with a patient fourteen days previously. There were nineteen days between the onsets in Cases 44 and 45 (mother and daughter). Therefore, from these few observations, it seems likely that the incubation period is between one and three weeks, with an average in most cases of about a fortnight.

The disease did not appear to spread through families, as some other infectious diseases do. In only three incidents in this series were there two cases in the same household. This suggests a mode of spread and perhaps immunity, as occur in poliomyelitis today.

I gained the impression that new persons entering the district seemed susceptible to the disease. Four of the patients in this series came from outside the district. Two patients (Cases 22 and 23) were Italian fruit pickers. One patient (Case 7) had arrived on a river launch just prior to the outbreak, and another (Case 40) had three weeks previously come from Geelong, Victoria. Perhaps this is a small figure in a community with a floating population of fruit pickers; but, as was stated before, many persons who also may have recently entered the area probably had the illness and did not report.

As the outbreak was nearing its end—i.e., at the beginning and middle of May—the illness appeared to change character somewhat. The rash often appeared less definite; in fact, in some cases the illness continued for two weeks. Often the joint symptoms were minimal, and in view of the presence of the epidemic, these cases were suspected as perhaps variants. It is suggested that a general community resistance could account for these cases, as the outbreak was nearing its close.

This series of cases was collected from the outbreak at Renmark only; but from personal communication with medical men from the other nearby river towns (Berri, Barmera and Loxton) it is known that similar outbreaks occurred in all these areas, including Mildura and other Victorian towns (Anderson and French, 1957).

The features of the illness in these surrounding areas were exactly similar to our own cases, and need no further comment except that the suggestion has been made that on Easter Monday, at the beginning of the outbreak, a large crowd of 7000 from all the Murray districts collected at Lake Bonney at Barmera for an Easter regatta, and this could easily have provided an excellent focus for the initial outbreak. In Renmark itself, no local area seemed to be particularly involved. Cases occurred in all areas of the town and settlement alike. Also there seemed no occupational predilection, as cases occurred in all sections of the community. It was thought at one stage that fruit growing or the handling of fruit could be a factor common to all; but this proved subsequently to be definitely not so. The patient in Case 40 volunteered the information that her house seemed to be unusually plagued with mice at the time of the outbreak. This was the only patient who gave this information, and from general reports at that time of the year, the mice were no more plentiful than usual. Subsequently, however, as the flood water rose, mice were only too plentiful, being driven from their usual abode into the isolated town. When we considered the possibility of a mouse-borne infection, a typhus-like illness and rickettsial pox both suggested themselves; but the clinical picture far from fulfilled the criteria for these diagnoses.

Aetiology and Epidemiology.

In a search for a possible epidemiological basis for the outbreak, the rainfall in the area was studied. It was found that the rainfall for the year had been far in excess of the usual amount. The average rainfall is nine and a half inches *per annum*, and it was seen that this figure was reached mid-way through July, the maximum monthly fall (242 points) having occurred in the month of April.

It must be more than a matter of mere coincidence that the outbreak occurred in the month of maximum rainfall in an exceptionally wet season. Perhaps, as is seen with

Murray Valley encephalitis, the obvious increase in bird life and insect vectors may have some bearing on the problem.

As 1956 proved to be the year of the most disastrous flood in Renmark's history, a recording of the river levels was obtained. The river normally stands at nineteen feet four inches to nineteen feet six inches, and in the month of April it rose from nineteen feet seven inches to twenty feet one inch—i.e., only a few inches above its usual level. Subsequently in that year the river rose steadily, and reached an all-time peak of thirty feet seven and a quarter inches on August 22, 1956, with great loss of land and homes all along the river.

The outbreak occurred before this mass of water entered the area, and therefore seems to have no direct bearing on the problem. It will be interesting to see what eventuates when the surging flood goes down, leaving a great mass of stagnant water, ideal for animal and insect life.

This occurrence of excessive rainfall, and the appearance of mosquitoes at the time, are in accordance with reports of other epidemics of a similar nature, which also occurred in wet seasons. A study of the literature reveals three articles, all in THE MEDICAL JOURNAL OF AUSTRALIA, of an illness of epidemic polyarthritis (Halliday and Horan, 1943; Sibree, 1944; Dowling, 1942). These epidemics had many features in common with the present epidemic, and could very likely be the same disease. These authors all describe an illness in which the polyarthritis is the presenting symptom. Although in an occasional case the joint features were absent, on the whole they were the main feature of these outbreaks. In the cases here reported, as was stated previously, the rash was always the presenting and main feature of the complaint, and joint symptoms were seen in only one-third of the number.

Halliday and Horan, Sibree and Dowling all describe an illness somewhat more prolonged and incapacitating than that seen in the present series. Only a few of their patients were able to continue work, and most were in bed for a week or so and some even for as long as four weeks. The rash they describe is similar to that in the present series; but they state definitely that it did not occur in all cases, and its site of onset varies with each reference. The occurrence of adenitis and that of itching of the rash also are variable, but a fever seems to be a more constant feature in their cases. However, it is the range, extent and severity of the polyarthritis, far in excess of that seen in our outbreak, that is the chief differentiating feature.

The Murray Valley distribution of the disease is interesting, and must surely be of some significance. The distribution is very similar to that of Murray Valley encephalitis, as has been previously reported by Miles and Howse (1953) in this journal. By analogy with this interesting work, it is suggested that a similar epidemiology may be the cause of our Murray Valley rash. There is much in favour of the virus theory, as seen in the explosive nature of the outbreak, the occurrence of milder cases at the close of the epidemic, and the general features of the disease. The obvious increase in bird life and mosquitoes, owing to the wet season, is strongly supporting evidence for spread by infective animal and insect vectors, much in the way Murray Valley encephalitis was spread.

Another vector that may possibly be concerned is the biting fly *Austrosimulium furiosum* of the Simuliidae family. Anderson and French (1957) have mentioned the possibility that this fly may be the insect vector, in view of the connexion with certain outbreaks of polyarthritis.

This fly was seen in Renmark very prominently about the month of September, 1956, when much stagnant and flowing water was about the area during this flood period. There were many sufferers from the bites of this fly. Those seen were mostly persons working outside on their fruit blocks. The bites were mainly on the legs, and were large vesicles varying in size from half an inch to several inches in diameter. There was a surrounding

area of erythema, and the vesicles contained a thick mucoid substance. The vesicles would burst, and a necrotic slough would eventually separate. No other sequela or effect of these biting flies were noted in the area.

As this Murray Valley rash occurred in April and the flies were not seen until September, I believe it is unlikely that there is any connexion between the two outbreaks.

The original explosive outbreak could be explained by the crowding of susceptibles within an area in which the virus reservoir was situated at a time when a large number of insect vectors were present. The subsequent spread of the disease could be achieved by the dissemination of infective animals and birds or human beings to other areas, where there were vectors sufficiently numerous to propagate the disease; or the subsequent spread could possibly be due to the dissemination of insect vectors themselves.

From these considerations, it appears sound to assume an infective agent as the cause of the outbreak, and therefore it is particularly disappointing that so far investigations have not, in this or in the epidemics of polyarthritis previously mentioned, isolated a causative virus.

Conclusion.

A description has been given of 45 cases of a rash occurring in Renmark, South Australia, in the Upper Murray area, in April-May, 1956. The clinical features have been described, and certain conclusions as to the epidemiology and aetiology of the disease have been reached.

It has been suggested that the illness is a viral infection, being spread by mosquitoes, and possibly with an animal origin in the bird life migrating to the fertile wet land of the Murray basin in this particularly wet season.

The literature has been reviewed, and the illness has been compared with three reported outbreaks of epidemic polyarthritis.

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HORMONAL THERAPY AND THE SIGNIFICANCE OF THE PREGNANEDIOL EXCRETION TEST IN RECURRENT ABORTION.¹

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AND

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RECURRENT, spontaneous abortion is still one of the most baffling problems facing the medical profession today, from both the aetiological and the therapeutic aspects.

During the past decade there has been a remarkable reduction in fetal mortality due to late complications of pregnancy and during labour. Unfortunately the fetal

¹ This work was made possible by grants to each of the authors from the National Health and Medical Research Council.

wastage from spontaneous unexpected abortion has not shared this reduction. The importance of the problem is stressed by the fact that this wastage is six to eight times greater than that from all the later complications of pregnancy combined.

A great number of causes have been suggested, but in most cases no conclusive proof has been established. It seems possible that in a certain number of cases there may be more than one aetiological factor, whilst in others there may be a non-recurring cause. It is well to bear this in mind when condemning any form of treatment which may fail to achieve its object in the pregnancy under consideration. It is most probable that no single therapeutic agent which would prove effective in all cases will be forthcoming.

In the normal menstrual cycle the *corpus luteum* is responsible for the production of progesterone for a period of ten to twelve days after ovulation. Some, but not all, of this progesterone is converted into pregnanediol and excreted in the urine as sodium pregnanediol glycuronide, which can be estimated by chemical methods. If no pregnancy intervenes, pregnanediol disappears from the urine in twelve to fourteen days after ovulation, and menstruation occurs. If pregnancy occurs, implantation of the fertilized ovum takes place about eight to ten days after ovulation, and almost immediately trophoblastic cells begin the production of chorionic gonadotropin, which can be detected in the urine in forty-eight hours. It appears to be responsible for the maintenance of the *corpus luteum* in early pregnancy, the latter continuing to produce progesterone and oestrogen. Late menstrual and early decidual changes of pregnancy merge into one another, there being no abrupt distinction. Similarly, no abrupt changes occur in the amount of pregnanediol excreted in the first few weeks of pregnancy.

From the study of abortion by many workers it seems probable that many early abortions may be associated with a defective conceptus. The entire ovum may be abnormal, or the abnormality may be localized to the trophoblastic component. In the latter case there is an inadequate production of gonadotropin, the normal delicate hormonal balance is upset, and the pregnancy fails to continue. This persistently low level of chorionic gonadotropin followed by a fall in urinary pregnanediol excretion may precede the onset of signs or symptoms of abortion. In such cases therapeutic measures are probably valueless; but it is almost impossible to diagnose such cases with an accuracy which would indicate that no treatment should be given.

The *corpus luteum* is generally considered to be active for a period of 70 to 100 days after its formation. Poorly developed trophoblastic cells may produce enough gonadotropin to maintain the *corpus luteum* for a period of time, but thereafter the developing placenta fails to produce sufficient progesterone to maintain the pregnancy, and abortion eventually occurs. It is suggested that substitution hormonal therapy is of value in these cases before signs or symptoms of impending miscarriage present themselves.

Hormonal deficiencies of different types have been the subject of much investigation as causes of recurrent abortion for many years. Smith and Smith (1934, 1937, 1938, 1939, 1940) have reported results of variations in the female sex hormones in relation to toxæmias of pregnancy and fetal mishaps. In their earlier papers they showed that the serum prolactin level was raised whilst the serum oestrogen content was decreased in many toxæmic pregnant women.

White and Hunt (1943) used the serum level of prolactin to predict the likelihood of toxæmia or fetal mishap in diabetic mothers. Later, Smith and Smith (1944) concluded that the rise in serum prolactin level which usually occurred in the latter part of pregnancy was the sequel to changes commencing much earlier in the pregnancy. They thought that hormonal treatment at that stage had little effect on arresting abortion. Later investigations (1946, 1948) led them to conclude that the administration of stilboestrol acted as a stimulus for the production of pro-

gesterone. The evidence leading to this conclusion was demonstrated by increased excretion of pregnanediol in the urine after ingestion of stilboestrol and a decrease when its administration was discontinued. These workers also reported considerable success in the treatment of patients who had had recurrent abortions by increasing doses of stilboestrol from the early weeks of pregnancy to the thirty-fifth week.

In 1947 work on pregnanediol excretion in relation to toxæmias of pregnancy was commenced at this hospital, and in 1949 it was decided to investigate the claims of Smith and Smith regarding the value of stilboestrol and to correlate the clinical findings with the pregnanediol excretion in cases of recurrent abortion. In Part I of this paper the method used for the estimation of the pregnanediol excretion per twenty-four hours in normal pregnant women is described. The average daily excretion and the range of excretion in these patients are reported. In Part II the excretion of pregnanediol throughout pregnancy of a series of women who had a history of recurrent abortion is given. The Smith and Smith stilboestrol therapy is discussed in relation to both its effects on pregnanediol excretion and the results of the pregnancy in a similar group of patients. The effects of *corpus luteum* therapy both alone and in combination with stilboestrol on other patients of the same type are also reported.

PART I: ESTIMATION OF PREGNANEDIOL AND ITS EXCRETION IN NORMAL PREGNANT WOMEN.

Estimation of Pregnanediol.

Various methods of pregnanediol estimation have been tried in this laboratory, including the Venning gravimetric method (1937), the Allen and Viergiver glycuronide method (1941), and the Guterman method (1944).

Williams's Modification (1950) of Somerville, Gough and Marrian's Method (1948).

The Williams modification may be summarized as follows:

A volume from a twenty-four-hour specimen of urine estimated to contain approximately two milligrammes of pregnanediol is hydrolysed and extracted by boiling under a reflux with concentrated hydrochloric acid and toluene. The urine is extracted once more by vigorous shaking with toluene. The combined toluene extracts are washed twice with sodium hydroxide and then with water until free from alkali. The washed extract is evaporated to dryness.

The residue is dissolved in four millilitres of absolute alcohol and then precipitated by the addition of 16 millilitres of 0.1 N sodium hydroxide solution. After incubation overnight it is treated with "Supercell" and finally centrifuged for thirty minutes. The residue, dissolved in absolute alcohol, is reprecipitated under the same conditions, with the substitution of 16 millilitres of distilled water for the 0.1 N sodium hydroxide solution. After incubation for two hours the mixture is centrifuged for thirty minutes. The residue is treated with five millilitres of absolute alcohol in a water bath at 75°C. for one minute, and then filtered quantitatively (Whatman Number 2 paper) into a weighed tube. It has been found so difficult to obtain animal charcoal which neither absorbs pregnanediol nor adds extraneous material to the alcoholic extract that this step in Williams's method has been eliminated. The filtrate is evaporated to dryness and the tube and residue are dried in a vacuum desiccator to constant weight. The amount of pregnanediol excreted per day is calculated.

Comparison of the Results Obtained by Estimating the Pregnanediol Residue by (i) Gravimetric and (ii) Colorimetric Technique.

One of the chief difficulties in the application of controlled hormonal therapy to combat recurrent abortion is the length of time required for each pregnanediol estimation. Since a few comparison experiments by Williams had shown that the gravimetric and colorimetric estimates did not vary greatly, it was decided to use the gravimetric technique. The colorimetric method has two disadvantages: (i) the time to obtain results is increased; (ii) concentrated sulphuric acid is unpleasant to handle.

Kerley (1952) has shown that applying the colour reaction to the weighed pregnanediol residue has given almost identical amounts of pregnanediol by either method. Both gravimetric and colorimetric methods were carried out on 39 specimens, each in duplicate. In only seven out of 78 estimations did the results by the two methods differ by one milligramme or more when the pregnanediol concentration fell between two and four milligrammes. The average difference in the other 71 was 0.4 milligramme when the total amount of pregnanediol was of the same order. In nine tests the concentration of pregnanediol by both methods was identical, in 39 tests the colorimetric method gave a slightly higher concentration, and in 30 the colorimetric values were slightly lower.

These observations are open to two interpretations—either that not all of the residue is pregnanediol or that extraneous substances precipitated with the pregnanediol give a similar yellow colour with concentrated sulphuric acid in the majority of assays. The colorimetric method therefore offers no greater accuracy than the gravimetric method. It might be added that these findings were contrary to those of Smith, who found much lower results by the colorimetric assay. The colorimetric estimation is of value in checking gravimetric results which appear too high, or when poor duplicates in gravimetric tests are obtained.

Petroleum Ether Extraction to Remove Chromogens.

Smith (1950) reported that in urine from pregnant women there were non-specific chromogens which could be removed by extracting the first pregnanediol precipitate in the Somerville, Gough and Marrian method with petroleum ether. In this laboratory Freeman (1950) applied the petroleum ether extraction to the final residue obtained by the Williams modification of the Somerville method. The residue was treated with 10 millilitres of petroleum ether for two minutes in a boiling water bath and then left for two hours. After centrifugation and removal of the supernatant fluid the procedure was repeated. The final residue was dried under vacuum and weighed.

Statistical analysis of the results from a series of such tests revealed that the variance between duplicates was mainly due to variation in pregnanediol and only about 30% was due to variation in the extractives. Further, the amount of extractives was found to differ significantly between the different tests. It has been noticed that residues from strongly pigmented urine are often deeply coloured, and also that the amount of pigment extracted in duplicate tests sometimes varies considerably.

Kerley (1952) has shown that under the conditions of petroleum ether extraction used by Freeman, pregnanediol itself is soluble. With pregnanediol concentration equivalent to five milligrammes per twenty-four hours there was a 30% to 35% loss, with two to three milligrammes per twenty-four hours, 30% loss, and with one milligramme per twenty-four hours, 20% loss, which was not significant. The Smith method of washing with cold petroleum ether produced negligible loss with a concentration of one to two milligrammes of pregnanediol per twenty-four hours, and 15% loss with the excretion of five milligrammes of pregnanediol per twenty-four hours.

In only five of 29 pairs of duplicate assays were pregnanediol values significantly lowered and the duplicates in closer agreement after the Freeman petroleum ether treatment. We have not been able to obtain direct evidence that the petroleum ether removes other extractives. It therefore seems reasonable to assume that the extra time involved in applying the extraction with petroleum ether is not warranted.

Comment.

Since this work was completed, the method of Kloppe, Michie and Brown (1955) has been published. Two steps in their method seem worthy of incorporation into that outlined in this paper. We have found that washing the toluene extract with 25% sodium chloride solution in the normal sodium hydroxide solution is invaluable in breaking

down the emulsion which so frequently occurs. This allows for a much cleaner separation of the aqueous and toluene layers.

The other step is the washing of the toluene extract with 4% permanganate solution in normal sodium hydroxide solution to remove chromogenic contaminants such as pregnanetriol. Although this substance is more likely to occur in the urine from men, it is possible that such derivatives may occur to some extent in the urine of some if not all women.

No extra time will be added to the Williams method, since these two washes can be substituted for those with normal sodium hydroxide solution.

Unfortunately the Kloppe method does not decrease the time in which the result can be obtained. It is possible that it may give a more accurate determination of very small amounts of pregnanediol. However, in following the value of progesterone treatment the variations are of greater order of magnitude.

Summary.

From the data reported above it seems reasonable to use the gravimetric technique in Williams's modification of the Somerville, Gough and Marrian method for most of the specimens assayed. If duplicate tests show wide divergence in the weights of the residue, or when there is pronounced increase in pregnanediol in two consecutive tests, application of the sulphuric acid colorimetric method is useful in confirming the gravimetric result.

Petroleum ether extraction applied to residues contaminated by urinary pigments does not appear to provide a more accurate estimate.

Excretion of Pregnanediol in the Urine of Normal Pregnant Women.

At the commencement of this work, Venning's figures for the excretion of pregnanediol by normal pregnant women were the only ones available. These were obtained by gravimetric assay of sodium pregnanediol glycuronide after butanol extraction of twenty-four hour specimens of urine from eight normal pregnant women at monthly intervals throughout the pregnancy.

It seemed advisable to obtain a curve for the average normal pregnanediol excretion by the method used in this investigation. We therefore assayed over 300 twenty-four hour specimens from women who were normal at the time of assay and gave a history of no previous obstetric complication. The series was reduced to 275 by elimination of results of tests on patients who later developed toxæmia or had premature labour or miscarriage. In most instances three specimens were obtained from each patient at weekly intervals.

The curve for the average level for excretion of pregnanediol and the 95% probability range are illustrated in Figure 1. It will be observed that there is a wide variation in the pregnanediol excretion of different women who have a normal pregnancy. Venning's figures revealed similar variations, as did a recent series reported by Michie (1953). The average level for pregnanediol excretion throughout normal pregnancy in our series is shown in Table I.

PART II: CLINICAL AND LABORATORY INVESTIGATION OF THE EFFECT OF HORMONAL THERAPY.

In 1948, Smith, Smith and Hurwitz stimulated new interest in the problem of recurrent abortion by claiming considerable success after the administration of increasing doses of stilbæstrol for this condition. Other workers (Crowder *et alii*, 1950; Davis and Fugo, 1948; Dieckmann *et alii*, 1953; Karnaky, 1949; Robinson and Shettles, 1952; Seitchik, 1950; Snaith, 1950; and Somerville *et alii*, 1949) subsequently confirmed or challenged these results. It was decided to determine the effect of stilbæstrol in recurrent abortions from both clinical and laboratory aspects in this hospital. Because of the results obtained, other methods of hormonal treatment were also investigated.

Nature of Investigation.

In 1949 an investigation was commenced at the Royal Women's Hospital, Melbourne, to obtain additional information about the problem of recurrent abortion. The work of Smith, Smith and Hurwitz (1946 and 1948) was based on the theory that stilbæstrol was a stimulator or precursor of progesterone production. Therefore close attention was paid to the urinary pregnanediol excretion test, for one would expect end products of progesterone metabolism to increase by the exhibition of stilbæstrol, if indeed this theory was correct.

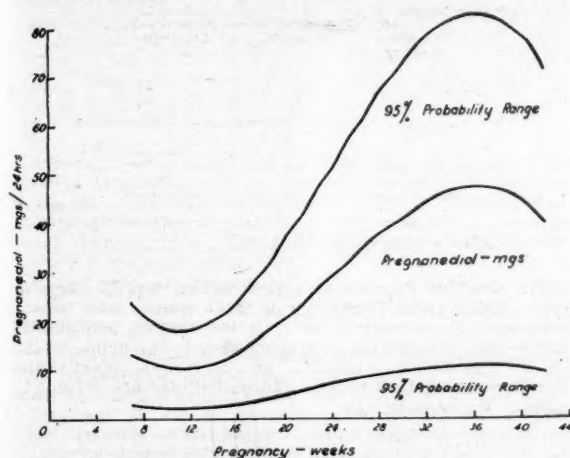


FIGURE 1.

Habitual or recurrent abortion now seems to be generally accepted as a condition in which three or more consecutive abortions occur without intervening pregnancies going beyond the twenty-eighth week of gestation. Many investigators (Smith *et alii*, 1948; Bishop and Richards, 1952; Malpas, 1938; and Eastman, 1947) have included two

TABLE I.
Daily Pregnanediol Excretion During Normal Pregnancy.

Weeks Pregnant.	Milli-grammes of Pregnanediol per Day.	Weeks Pregnant.	Milli-grammes of Pregnanediol per Day.	Weeks Pregnant.	Milli-grammes of Pregnanediol per Day.
7	13.6	19	18.5	31	42.2
8	12.3	20	20.3	32	43.5
9	11.8	21	22.5	33	44.5
10	10.6	22	24.6	34	45.3
11	10.2	23	26.6	35	46.0
12	10.3	24	28.7	36	46.3
13	10.6	25	30.8	37	46.2
14	11.3	26	33.0	38	45.8
15	12.5	27	35.0	39	44.8
16	13.6	28	37.0	40	43.5
17	15.0	29	38.9	41	41.8
18	16.6	30	40.6	42	39.8

previous consecutive abortions in their reports, and, to enable a comparison of results to be made, such cases have also been included in this series (see Table II).

One hundred and forty-four women giving a history of recurrent abortion were selected from those presenting as pregnant at the antenatal clinics. They had received no special investigation as to the possible cause of previous abortions, nor did they receive any treatment prior to becoming pregnant. Thereafter they attended a special clinic, and were divided into the following four groups: Group I: controls, to receive no treatment; Group II: to be given stilbæstrol therapy as suggested by Smith and Smith; Group III: to receive *corpus luteum* hormone, prin-

cipally as ethisterone given orally; Group IV: to receive the Smith regime, supplemented by *corpus luteum* hormone if the urinary pregnanediol excretion test revealed a persistently low or falling excretion.

Results of Investigation.

Although the figures presented, when subdivided into four groups, are insufficient for statistically significant conclusions to be drawn, a detailed study of the clinical results is interesting. The abortion rate for the whole series of 144 patients was 39 or 27% (Table II).

TABLE II.
Total Abortions.

Number of Successive Preceding Abortions.	Number of Patients.	Number of Abortions.
2	63	19
3	44	12
4 or more	37	8
Total	144	39 (27%)

Table III compares our results with those of Smith and Smith after stilbæstrol therapy. Stilbæstrol was given in doses increasing from five milligrammes per day at the sixth week to 115 milligrammes per day at the thirty-fifth week. There were 20 abortions among the 53 treated patients, as compared with 25 abortions among 127 patients in the Smith group.

A study of Tables III and IV shows that: (i) 20 patients or 38% treated with stilbæstrol alone, miscarried; (ii) nine out of 44 patients or 20% who received no treatment miscarried.

TABLE III.
Results of Stilbæstrol Therapy.

Number of Successive Preceding Abortions.	The Royal Women's Hospital, Melbourne.		Smith, America.	
	Number of Patients.	Number of Abortions.	Number of Patients.	Number of Abortions.
2	23	7	67	11
3	17	7	38	5
4 or more	13	6	22	9
Total	53	20 (38%)	127	25 (20%)

After a sequence of 53 patients had been studied and no decrease in the abortion rate had been observed, it was decided to proceed no further with this form of therapy, but to investigate the effect of *corpus luteum* hormone treatment both on its own and in combination with stilbæstrol. The results of these forms of therapy are shown in Tables V and VI. The overall success rate was approximately the same in both groups.

Corpus luteum hormones can be given in three forms: (i) as injectable progesterone; (ii) as progesterone implants; (iii) sublingually, for example, ethisterone. It is impracticable to give daily injections of progesterone, and anything less than daily injections probably have little therapeutic value, as excretion is mostly complete within twenty-four hours. Thus even daily injections are associated with an undesirable rise and fall in the blood level of progesterone.

A fairly constant blood level is held to be produced by implants, but it was considered preferable to avoid this minor surgical intervention if possible. In this hospital implants have proved very disappointing. These results will be reported in a subsequent paper.

We considered that if ethisterone was adequately absorbed, it could easily be administered at home at regular intervals, and that this would prove the most satisfactory method of treatment.

TABLE IV.
No Treatment.

Number of Successive Preceding Abortions.	Number of Patients.	Number of Abortions.
2	21	7
3	14	2
4 or more	9	0
Total ..	44	9

The only apparent justification for the use of injectable progesterone would appear to be in the treatment of patients suffering from severe *hyperemesis gravidarum* or some other conditions rendering sublingual or oral therapy valueless.

After ethisterone therapy had been begun, it was soon evident that we could raise the level of pregnanediol excretion, whereas we had not been able to do so with stilboestrol.

TABLE V.
Results of Corpus Luteum Hormone Therapy.

Number of Successive Preceding Abortions.	Number of Patients.	Number of Abortions.
2	11	2
3	7	2
4 or more	11	2
Total ..	29	6

When the effect of treatment is being determined, the "spontaneous cure" and expected abortion rates have to be taken into consideration. The figures of Malpas (1938), of Eastman (1947) and of Stallworthy (1955) for "spontaneous cure" are interesting and have been correlated in Table VII.

The comparable figures in our series for a group of patients selected at random and given no treatment show a reverse trend (Table IV). In our small series of 44 patients, the greater the number of preceding abortions, the better the outlook for the pregnancy under review. The results in the group receiving *corpus luteum* treatment regulated by the amount of pregnanediol excreted show that this hormone is effective in preventing abortion in many cases, and are supported by the findings of Bishop and Richards (1952), who used progesterone implants. Further, the success rate is not improved by the addition of oestrogen.

Although oestrogens are used prophylactically for the suppression of breast milk after labour, no cases were encountered in which breast feeding was adversely affected in patients taking large doses of stilboestrol right up to the onset of labour.

Significance of Urinary Pregnanediol Excretion.

In the series of 144 patients presented, 91 were subjected to urinary pregnanediol estimations. These tests were performed at weekly intervals until the thirty-sixth week of gestation, unless abortion intervened. Some patients had as many as 30 tests during their pregnancies, and over 1500 tests were performed.

TABLE VI.
Results of Combined Stilboestrol and Corpus Luteum Hormone Therapy.

Number of Successive Preceding Abortions.	Number of Patients.	Number of Abortions.
2	8	3
3	6	1
4 or more	4	0
Total ..	18	4

The abortion rate for the whole series was 39 cases or 27% (Table II). Thirty-two of these women had weekly pregnanediol estimations, and twelve showed persistently low or falling excretion of pregnanediol in the urine, whilst there was some evidence of decreased pregnanediol excretion in another twelve. These findings are set out in tabular form as follows:

Pregnancies terminating in abortion during which urinary pregnanediol excretion tests were performed	32
Persistent progesterone deficiency	12
Some progesterone deficiency	12
No progesterone deficiency	8

TABLE VII.

Number of Previous Abortions.	Percentage of Patients Expected to Abort.		"Spontaneous Cure": Percentage.		
	Eastman.	Malpas.	Eastman.	Malpas.	Stallworthy.
0	10.0	—	90.0	—	—
1	13.2	—	86.8	—	50
2	36.9	—	63.1	—	20
3	83.6	—	16.4	—	10
4	—	93	—	6	—

This observation is important, in that it indicates that there is a gross progesterone deficiency in about one-third and a milder degree in another one-third of the patients who have repeated miscarriage.

While we were reviewing the patients who had pregnanediol excretion tests performed during their pregnancies, the following facts emerged (Table VIII).

1. Normal pregnanediol excretion was persistently found in 29 patients, while 62 patients excreted an amount below the normal expectation at some stage during their pregnancy.

2. In the group with normal pregnanediol excretion a significantly larger number of pregnancies advanced to viability of the foetus than ended in miscarriage. The withholding of treatment would therefore appear justified in these cases.

3. In the group in which low excretion of pregnanediol was found there were more miscarriages than successful pregnancies among the untreated mothers.

4. In almost all patients treated with oestrogens and *corpus luteum* combined, low pregnanediol excretion occurred at some stage in the pregnancy. In many of these cases *corpus luteum* therapy was added only after

TABLE VIII.
Results of Treatment in Relation to Pregnanediol Tests.

Group.	Total Number of Patients.	Normal Results.		Some Low Results. ¹		Total.	
		Viable Fetus.	Miscarriage.	Viable Fetus.	Miscarriage.	Viable Fetus.	Miscarriage.
No treatment	21	10	2	3	6	13	8
Smith and Smith method	34	9	6	9	10	18	16
Corpus luteum treatment	19	1	—	14	4	15	4
Smith and Smith method plus corpus luteum	17 } ³⁶	1	—	12	4	13	4
Total	91	21	8	38	24	59	32

¹ "Some" indicates at least two.

falling or low pregnanediol excretion was found with stilboestrol treatment alone. The addition of this hormone produced a considerable increase in the number of pregnancies proceeding to viability of the fetus, the percentage being approximately the same as when corpus luteum hormone was used alone.

5. The pregnancy of 32 patients ended in miscarriage. In 24 some evidence of low pregnanediol excretion was obtained.

6. Thirty-six patients received corpus luteum treatment. The pregnancy proceeded to viability in 28. This compares most favourably with the results of oestrogen therapy alone, when only 18 out of 34 pregnancies proceeded to foetal viability, and with the spontaneous cure rate in the untreated patients—namely, 13 out of 21. Other suggestive evidence that progesterone insufficiency may result in miscarriage was procured in serial pregnanediol tests on a small series of women who gave a history of miscarriages, but who also had living children. Six patients had normal pregnanediol excretion throughout the pregnancy under review; only one miscarried. Similarly, when corpus luteum therapy was given to five with low pregnanediol excretion, all had living children, except one patient whose treatment commenced only two days before she aborted. Pregnanediol excretion was low in six patients threatening to abort. Falling pregnanediol excretion was observed prior to one miscarriage. Stilboestrol therapy failed to raise the pregnanediol excretion and did not prevent miscarriage in two patients. Three patients given progesterone treatment recovered and later had living babies.

Clinical Detail of Cases Represented in Figures II to IX.

The following clinical histories are included to support the graphs. The normal level of excretion is included for comparison.

Falling Urinary Pregnanediol Excretion Preceding Miscarriage (Figure II).

Mrs. B. had undergone a thyroidectomy thirteen years before, and was taking two grains of thyroid daily. She had no living children and had had two previous miscarriages at three months' gestation. She was given no treatment, as the pregnanediol excretion was within normal limits. However, the day after the lower level was known, a discharge of blood-stained fluid occurred, and she once again miscarried at twelve weeks.

Mrs. C. was Rh-negative. She had had two previous miscarriages, at seven months and six months respectively. Excretion tests were commenced at twenty weeks. At twenty-three weeks foetal movements were doubtful, and the rapidly falling excretion suggested intrauterine death and placental insufficiency. The patient expelled a seven-ounce stillborn fetus two weeks after the last test, when the Rh incomplete antibody titre was 128.

Failure of Stilboestrol to Improve Pregnanediol Excretion (Figure III).

Mrs. L. had had two previous miscarriages, at four months and four and a half months respectively. The graph in

Figure III illustrates the persistently low excretion of pregnanediol in spite of massive doses of stilboestrol. The patient was receiving 90 milligrammes daily at the twenty-first week, compared with the recommended dosage of 60

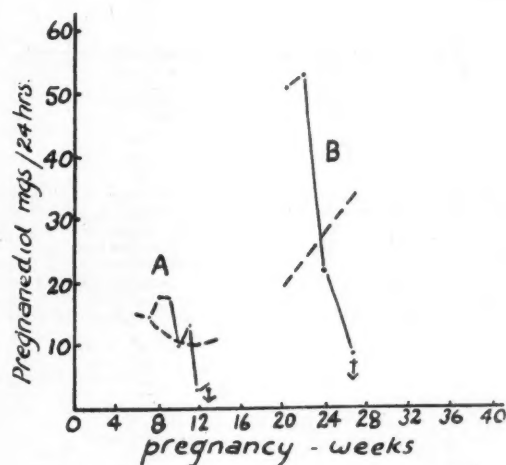


FIGURE II.

milligrammes at this stage. In spite of this treatment, the pregnanediol excretion was only about five milligrammes per twenty-four hours, or one-quarter of the normal average output. She eventually miscarried at twenty-five weeks while taking 110 milligrammes per day.

Response of Pregnanediol Excretion to Ethisterone Therapy (Figure IV).

Mrs. K. had had four previous consecutive miscarriages at three months within the last four years. There were no apparent reasons for this history. She presented late in 1951 when eight weeks pregnant, and two weeks later her excretion of pregnanediol was normal. However, thereafter it fell, and at thirteen weeks the administration of 5.0 milligrammes of ethisterone per day was commenced, with an immediate response in excretion level. Because of a further fall at eighteen weeks, the ethisterone dosage was doubled, and at twenty weeks the administration of 20 milligrammes per day was commenced, with an excellent response. The pregnanediol level remained normal with this dosage. At twenty-six weeks rupture of the membranes occurred, and one week later a one-pound baby was delivered by the breech; the infant survived for twenty-four hours.

A similar response to corpus luteum hormone in the urinary pregnanediol excretion level was demonstrated in many other cases. Such responses have not been obtained with the Smith stilboestrol regime.

Falling Pregnanediol Excretion after Cessation of Ethisterone Therapy (Figure V).

Mrs. E. reported in December, 1949, with the following history: two miscarriages at nine weeks in 1945, a normal living child in 1947, and a miscarriage at fourteen weeks in 1948. She was placed on the Smith regime at six weeks,

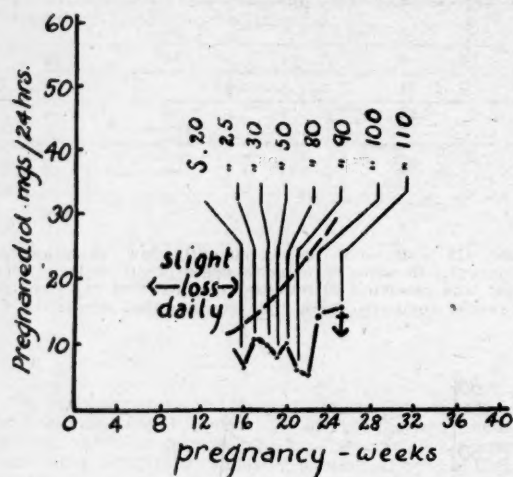


FIGURE III.

and the results of pregnanediol excretion tests were within normal limits. Nevertheless, she miscarried at twenty-one weeks. She reported again in 1951, and when she was six weeks pregnant, 10 milligrammes of ethisterone were given three times a week. At ten weeks the excretion of pregnanediol was so far above normal that treatment was suspended. The fall in level during the following four weeks is illustrated (Figure V). During this time treatment

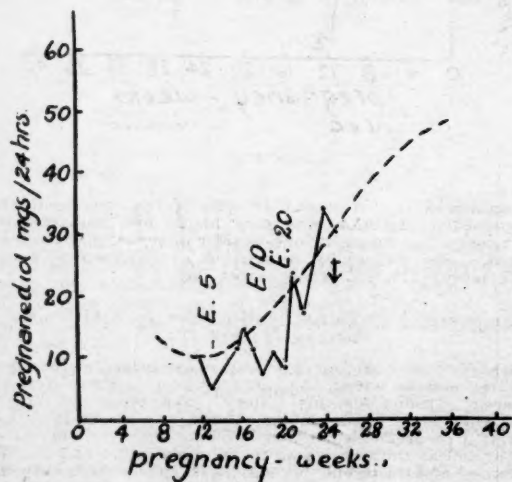


FIGURE IV.

was deliberately withheld. The level was temporarily raised by the further exhibition of ethisterone at fourteen weeks. The level was still below the average normal and she miscarried at seventeen and a half weeks.

Pregnancy Maintained by Large Doses of Ethisterone (Figure VI).

Mrs. O. reported in 1950 in early pregnancy, giving a history of miscarriages at three months in 1946, a full-term

infant the following year, and two miscarriages in 1949 at sixteen weeks and six weeks. She was placed on a full stilboestrol regime, but miscarried at six and a half months. In 1951 pregnancy again occurred, and at nine weeks a dosage of 10 milligrammes per day of ethisterone was introduced. This was increased to 20 milligrammes per day at

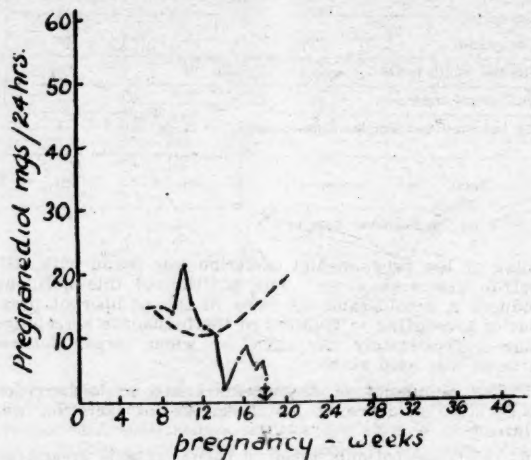


FIGURE V.

seventeen weeks and 40 milligrammes per day at twenty-three weeks. At twenty-nine weeks she was admitted to hospital for daily excretion tests for a period of ten days. At thirty-one weeks the ethisterone dosage was increased to 75 milligrammes per day and a steady rise occurred to thirty-five weeks, when she came into spontaneous premature labour and was delivered of an infant weighing five pounds seven ounces, alive and well.

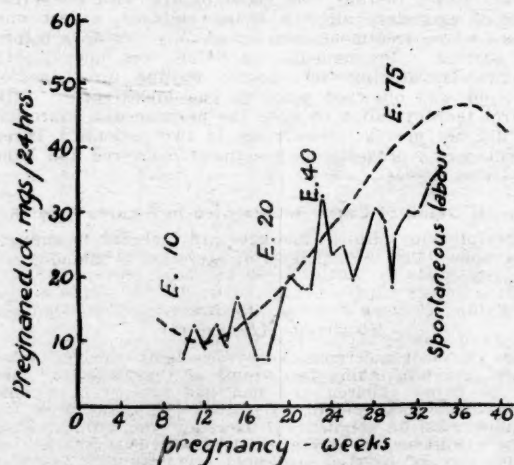


FIGURE VI.

In the latter half of this patient's pregnancy the level of excretion was extremely low; but it was held there by the exhibition of *corpus luteum* extract, without which it is believed that the pregnancy would almost certainly have ended in failure.

Maintenance of Pregnancy by Ethisterone Therapy (Figure VII).

Mrs. A. illustrates a somewhat similar type of case. She had had four previous consecutive miscarriages at three months, and no living children. She presented to the out-

patient department in 1951, and was given 10 milligrammes of ethisterone daily when six weeks pregnant. This was raised to 30 milligrammes per day as the pregnancy advanced. Her pregnanediol excretion remained at a disturbingly low level throughout, but she went on to term,

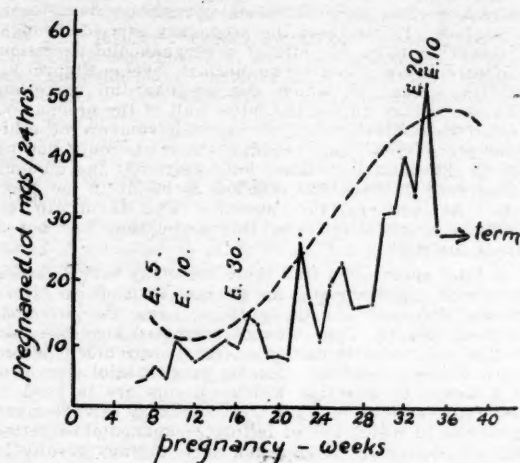


FIGURE VII.

when a normal male infant weighing six pounds seven ounces was delivered. It was noted that the placenta was only approximately half the normal size, and this probably accounted for the low pregnanediol excretion.

Failure with Stilbæstrol in One Pregnancy: Success with Ethisterone in Following Pregnancy (Figure VIII).

Mrs. O. presented to the hospital in August, 1950, with the following history: a miscarriage at three months in 1945, a full-term infant in 1947, a miscarriage at six months

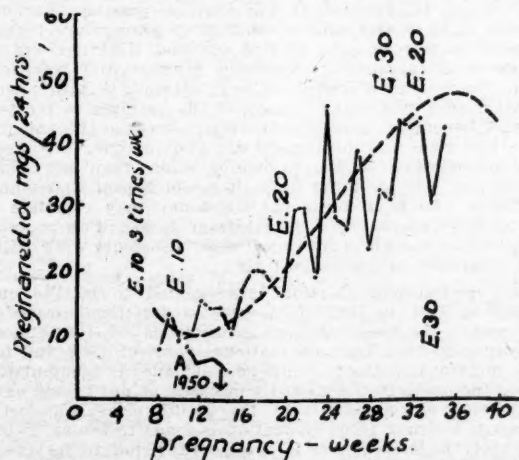


FIGURE VIII.

in March, 1949, and a miscarriage at two months in September, 1949. She was immediately placed on the stilbæstrol regime, but at fourteen weeks she miscarried, with a pregnanediol excretion falling to a low level. This made a total of three consecutive miscarriages in two years. In March, 1951, she again reported pregnant, and at six weeks was given ethisterone, 10 milligrammes three times per week. At ten weeks this was increased to 10 milligrammes per day, and her pregnanediol excretion remained at a normal level. At fifteen weeks, daily excretion tests

were performed, and although her excretion remained satisfactory, the ethisterone dosage was increased to 20 milligrammes per day at twenty weeks and to 30 milligrammes per day at thirty weeks. At thirty-four weeks the dose was reduced to 20 milligrammes per day and the excretion fell, but it rose when the dosage was increased again to 30 milligrammes per day. At thirty-eight weeks the pregnancy was terminated by artificial rupture of the membranes and a normal male baby was delivered.

Failure with Stilbæstrol and Immediate Success with Addition of Ethisterone (Figure IX).

The following case illustrates the type of patient who fails to respond to stilbæstrol, but who appears to respond to ethisterone.

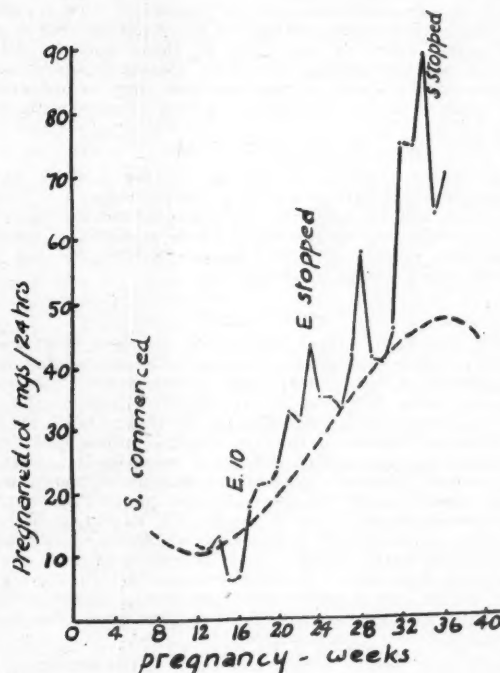


FIGURE IX.

In 1945 Mrs. D. had a normal pregnancy, but two years later one ovary was removed. Five months after this surgical procedure she miscarried when ten weeks pregnant, and in the following year two more early miscarriages occurred. Once more pregnancy became apparent late in 1950, and at five weeks increasing stilbæstrol therapy was commenced. In spite of this the pregnanediol excretion fell to the non-pregnant level at sixteen weeks, and the daily administration of 10 milligrammes of ethisterone was commenced in addition to the stilbæstrol. The response in pregnanediol excretion was so good that ethisterone treatment was stopped at twenty-three weeks, and she carried on with stilbæstrol alone to thirty-five weeks. She was delivered at term of a normal male baby weighing nine pounds eight and a half ounces. During labour her blood pressure rose to 165 millimetres of mercury, systolic, and 115 millimetres, diastolic, and her urine contained "two-thirds" albumin.

Onset of Miscarriage in the Treated Group.

In the group of patients who aborted in spite of treatment, an important feature noted was the late onset in a large proportion. Thirty-nine women aborted, and twenty-four did so between the sixteenth and twenty-sixth weeks of pregnancy. As it is generally believed that the most dangerous period is at the end of the first trimester, it is possible that the treatment given may have delayed the

abortion in this large proportion of cases. Whether more intensive hormonal therapy would have salvaged some of these pregnancies is a matter for conjecture at the present time.

Observation of Initial Sign of Impending Miscarriage.

Another interesting observation in the miscarriage group was the nature of onset in many patients. In 12 women out of 24 in whom miscarriage occurred after the sixteenth week, the first sign of impending miscarriage was the finding of membranes bulging through the external os, or actual premature rupture of the membranes. The cervix was frequently found to be about three centimetres dilated, with a large portion of membrane and liquor amnii bulging through. This was usually preceded by a short history of thin, white discharge, free of blood. There was absence of any abdominal pain or discomfort. There was no evidence to support a theory of hormonal deficiency in these cases, since in only two of these patients was excretion of pregnanediol decreased. No explanation can be given of the cause of this condition, nor as yet does there seem to be any therapeutic means of preventing it.

Foetal Abnormalities.

Pathological examination of all aborted fetuses and placenta was not carried out as a routine measure. However, there was no apparent macroscopic evidence of any foetal abnormalities in the whole group studied. It would appear that grossly abnormal fetuses will be aborted in the very early stages of pregnancy.

DISCUSSION.

Davis and Fugo (1948), and Somerville and co-workers (1949) failed to confirm the findings of Smith, Smith and Hurwitz (1946 and 1948) that pregnanediol excretion increased after ingestion of stilboestrol. Pregnanediol is excreted as sodium pregnanediol glycuronide; Smith, Smith and Hurwitz estimated the glycuronide radicle and then calculated the equivalent amount of pregnanediol. Since Dodson and Williams (1948) and Teague, Wingard and Brown (1949) found that 6% to 35% of ingested stilboestrol was excreted in the urine of the women, the apparent rise in pregnanediol excretion observed by Smith, Smith and Hurwitz, but not found by Somerville and co-workers, could be explained as being stilboestrol glycuronide. On the other hand, Smith and Schiller (1950) in a later paper proved that their sodium pregnanediol residues were free from all except traces of stilboestrol.

Smith and Barker (1952) showed that the difference in results obtained by the Venning and the Marrian methods was due to the presence of non-pregnanediol components included in the sodium pregnanediol complex of the Venning process. They found that these other metabolites of progesterone were consistently increased after ingestion of stilboestrol. They also found that continued therapy with either progesterone or stilboestrol was associated with increasing output of pregnanediol, pregnanolone and "x" steroid. A drop in all three occurred when therapy was interrupted.

In our investigation no increase in urinary pregnanediol excretion was observed in patients treated with stilboestrol. This is well shown in Figure II, in which it is seen that at the twenty-fifth week of gestation, and in spite of the administration of 110 milligrammes of stilboestrol per day, the urinary pregnanediol excretion was still only half the expected normal level, and abortion occurred at this time.

In some patients the Smith regime of stilboestrol therapy was begun as early as the sixth week, yet the pregnanediol excretion remained persistently low or continued to fall. On the other hand, when *corpus luteum* was introduced in addition to stilboestrol in such cases there was usually a pronounced, rapid, and well-sustained rise in pregnanediol excretion (Figures IV, VI, VII, VIII). In one instance (Figure V) 75 milligrammes of ethisterone per day were given at the thirtieth week without ill effect, and in some cases as much as 200 milligrammes per day were given without untoward side reactions.

The recovery of pregnanediol from urine did not appear to have any direct relationship with the amount of *corpus luteum* given, although an obvious rise in excretion was noted in most cases.

A low or falling level of pregnanediol excretion does not always predict an early end to the pregnancy, and conversely, a normal excretion does not always promise a viable infant. In six cases the pregnancy carried through to viability or later, in spite of a pregnanediol excretion persistently below the average normal level. Figure VI illustrates a case in which the pregnanediol excretion was below average during the latter half of the pregnancy. In spite of administration of 75 milligrammes of ethisterone per day, the pregnanediol excretion could not be raised to the normal average; but apparently the amount of ethisterone ingested was sufficient to maintain the pregnancy. At delivery the placenta was found to be abnormally small. However, this correlation was not a constant finding.

It is fully appreciated that there are many varied causes of recurrent abortion, and no attempt is made to stress hormonal deficiency as the only or even the principal aetiological factor. The evidence presented suggests that hormonal treatment is wasted on many patients in whom no such deficiency exists. Regular pregnanediol tests provide a means of detecting which patients are in need of *corpus luteum* therapy. Such treatment may salvage many pregnancies in which low or falling pregnanediol excretion levels are detected. Even when such therapy results in the correction of hormonal deficiency, miscarriage may still occur owing to the presence of other possible causative factors. However, one can hope for a significant improvement in the number of live births among women with this type of hormonal insufficiency. Further, the only satisfactory and scientific approach to the treatment of such patients is to determine the dosage of ethisterone in accordance with the amount of pregnanediol excreted. Unfortunately pregnanediol assays are not always able to be carried out in time to prevent threatened abortion. Ethisterone may be given empirically when they cannot be performed, particularly in the earliest part of pregnancy. A suggested dosage is 10 milligrammes per day until the twelfth week, and thereafter 20 to 30 milligrammes per day till the thirty-sixth week. This dosage can safely be doubled at the earliest possible moment should signs or symptoms of impending miscarriage reveal themselves. It must be pointed out that if ethisterone is given in the absence of control by pregnanediol excretion tests, the treatment should not be condemned because many miscarriages still occur. Many of the patients so treated cannot benefit by hormonal treatment because the amount of ethisterone may be inadequate, and in other instances the miscarriage is due to causes other than hormonal deficiency. On the other hand, it would appear that many patients who have hormonal deficiency may complete a satisfactory pregnancy if the arbitrary dosage of ethisterone happens to be sufficient to meet their deficiency even without control by pregnanediol tests.

As spontaneous abortion is estimated to be the end result in 10% to 15% of all pregnancies, the salvage of as many of these cases as possible is of the utmost importance, both from the national point of view and for the individual patient. Until new evidence is accumulated as to the cause in the majority of cases, or until some new, well-tested and more valuable therapeutic measure is forthcoming, a strong recommendation is made to return to the formerly popular *corpus luteum* therapy, but in increased and scientifically controlled dosage.

SUMMARY.

1. In our series the average pregnanediol excretion in normal pregnancy was somewhat lower from the twentieth to the thirty-fifth week of gestation than in the series reported by Venning.

2. The urinary pregnanediol excretion test, although complex and time-consuming, is a useful and reliable method for controlling *corpus luteum* therapy in habitual abortion.

3. Spontaneous abortion occurred in 39 cases or 27% of the series presented. Persistently low or falling excretion of pregnanediol was observed in 12 of these cases. There was evidence of some decrease in progesterone activity in 24.

4. A significantly low or falling excretion of pregnanediol does not invariably predict a disruption of pregnancy.

5. The results obtained by stilbesterol therapy, recommended by Smith *et alii*, were not reproduced. We could find no evidence to support their claim that stilbesterol stimulates or is a precursor of progesterone production.

6. The oral administration of ethisterone appears to be a satisfactory form of therapy for progesterone deficiency. In many cases in the present series it increased the pregnanediol excretion, and more pregnancies resulted in the birth of a living child.

7. Ethisterone appears to have no adverse effect on pregnancy when given in large doses, nor does it produce any undesirable side effects.

8. Twenty-four of the 39 miscarriages which occurred in this series of patients took place after the sixteenth week, when it is generally believed that a pregnancy is well established. In approximately half these cases the first indication was leaking or bulging membranes.

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Reports of Cases.

CONGENITAL RECTO-VAGINAL FISTULA IN AN ADOLESCENT.

By EDWARD WILSON, M.D., M.S., M.Sc., M.R.A.C.P., F.R.C.S. (England), F.R.C.S. (Edinburgh), F.A.C.S., F.R.A.C.S., Sydney.

Clinical Record.

WHEN she was first examined on December 16, 1955, Miss A., aged seventeen years, was suffering from an imperforate anus with an associated recto-vaginal fistula. She said that all her life the passage of faeces from the vagina had been practically continuous. When she was one year old an operation had been performed, but the details of this were not known. At the age of fourteen years an attempt had been made to construct a septum across the vagina in a coronal plane and thus divide the "cloaca" in two; but this was unsuccessful, and had only resulted in the formation of adhesions which partially covered the cervix. The opening of the recto-vaginal fistula just admitted the tip of the little finger and was situated two inches up the posterior vaginal wall (Figure 1). The patient's general health was good (she weighed 12 stone), and there was no other congenital abnormality. Her menstrual periods were regular, and her uterus and cervix appeared normal.

At operation on March 2, 1956, the rectum was separated from the vagina, and after the rectal opening had been enlarged it was transplanted to the perineum about two inches behind the vulva. During the operation the posterior vaginal wall and the perineum were incised in the mid-line

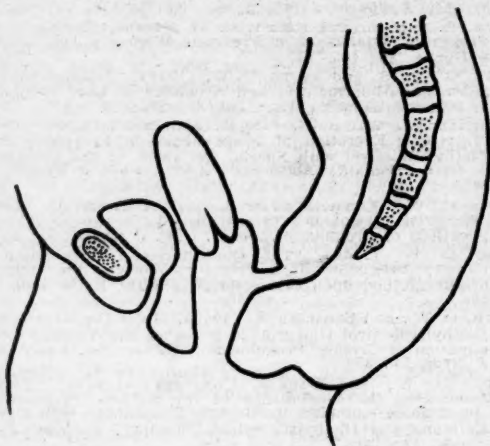


FIGURE I.

and the rectum was freed up to the peritoneum. The rectum was sutured to the perineal skin at the posterior end of the incision, which was then closed in layers (Figure II). Some fibres of the external sphincter muscles were seen during the operation. A drainage tube was inserted through the middle of the wound, and a transverse

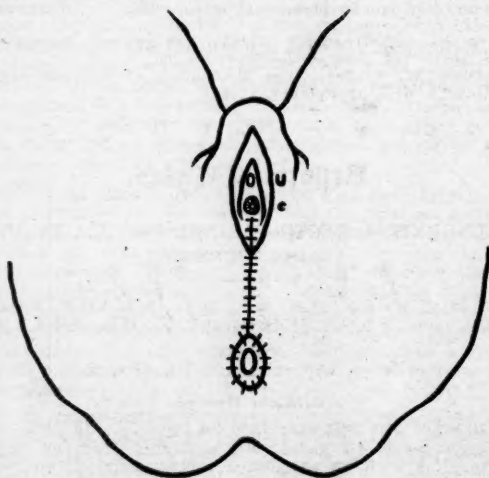


FIGURE II.

colostomy was then constructed. By the time the colostomy was closed on May 3, the perineal and vaginal wounds had healed and the end of the rectum was firmly adherent to the skin edges. Since then the bowels have acted once or twice a day. The patient is usually aware five or ten minutes in advance that a bowel action is imminent, and on most occasions is able to avoid soiling her clothes. However, control is less satisfactory in the presence of diarrhoea. The external opening of the rectum now just admits an index finger, and its appearance resembles that of a normal anus. The vulva and vagina also now appear normal.

Discussion.

This case is reported as an example of the commonest type of congenital malformation of the rectum and anus—that is, a type III abnormality (Ladd and Gross) with a recto-vaginal fistula. However, it is most unusual, in that the condition was not corrected until the age of seventeen years. This delay was due to the fact that the patient's parents had been advised that the previous ineffective operations represented all that was possible at the time. Fortunately, these previous operations had produced little scarring, and this did not interfere with the mobilization of the rectum. This operation was performed in much the same manner as in infants, but in this case the preparation of the colon with phthalyl sulphathiazole and orally administered streptomycin was more efficient than in most infants. In addition, the increased size of the bowel and other tissues facilitated the operation.

The final result of good control over the bowel, except when she is suffering from diarrhoea, and the normal appearance of the parts are very pleasing to the patient. While it is possible that just as satisfactory a result might have been attained without the diversionary colostomy, there is no doubt that such a colostomy could only aid the healing of the perineal wounds. The rapidity of healing of these wounds with the minimum of scarring was considered important in producing a satisfactory result, and more than outweighed the disadvantage of the relatively minor procedure necessary to close the colostomy. It is of note that no post-operative dilatation of the new anus has been necessary.

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Reviews.

The Child and the Outside World: Studies in Developing Relationships. By D. W. Winnicott, F.R.C.P.; edited by Janet Hardenberg, M.B.; 1957. London: Tavistock Publications, Limited. 8" x 5½", pp. 202. Price: 16s.

THIS is a companion volume to "The Child and the Family", but primarily written for the teacher and case worker. It is therefore more technical, though still expressed in fairly simple English that the average reading parent will also appreciate.

The book is divided into three sections—"The Care of Growing Children", "Children Under Stress", and "Reflections on Impulse in Children". No section attempts to be comprehensive, but each rather presents talks and broadcasts or articles in these fields. Dr. Winnicott is firmly convinced that nursery school teachers, doctors, nurses—in fact, everyone concerned in the care of young children—must be aware of the fundamental importance of the mother and appreciate her instinctual reactions. He also realizes how important it is for them to understand the reactions of the child at varying ages. In this respect the last section of the book is very helpful; infantile sexuality is simply explained; children's play, aggression and stealing and juvenile delinquency are sympathetically discussed.

Neither this book nor its companion is intended as a text-book, but rather as general literature on child study. It is easy to read, and all those interested in the rearing of children will gain by reading it, even if they do not always agree with conclusions reached by the author.

Modern Office Gynecology. By George Blinks, M.D., F.A.C.S., and Sherwin A. Kaufman, M.D., F.A.C.S.; 1957. Philadelphia: Lea and Febiger, Angus and Robertson. 7½" x 5½", pp. 220, with 47 illustrations. Price: 49s. 6d.

A BOOK which is comprehensive in its scope and yet presents the subject matter in a succinct and orderly manner is always welcome as a ready reference for everyday use, especially by the busy general practitioner. This is such a work. It is a small volume divided into three sections. In the first section, each chapter deals with a common gynecological symptom from the point of view of differential diagnosis, the clinical procedures necessary to make a diagnosis, and finally treatment of the various con-

ditions mentioned. Operative procedures, of course, are not described, controversial issues are avoided, and the therapy recommended is usually that found most effective by the authors. The second section of the book consists of a gallery of illustrations depicting procedures and techniques used in gynecological diagnosis and treatment; again all non-essential detail is omitted. These two sections in themselves constitute the usual type of book on so-called "office" gynecology. However, the volume has been improved, we believe, by the addition of a third section, which consists of a brief and up-to-date review of the subjects dealt with in the first section. It takes the form of an annotated bibliography, with references usually to readily available journals, together with clinical abstracts, and presents controversial issues and treatments including those opposed or at least not favoured by the authors themselves. An index completes the book.

The authors' intention has been to write a practical work on office gynecology, a ready reference book for the busy practitioner, and we think that they have accomplished this in a highly satisfactory manner. Perhaps the readability of the book would have been improved by eliminating the second section as such and incorporating and spacing the illustrations appropriately in the text, and even transferring the third section to the text as a series of footnotes; but this is only carping criticism of what appears to be a very handy little volume.

Clinical Toxicology: The Clinical Diagnosis and Treatment of Poisoning. By S. Locket, M.B., B.S., M.R.C.P. (London), with special sections by W. S. M. Griev, M.Sc., Ph.D., F.R.I.C., and S. G. Harrison, B.Sc.; 1956. London: Henry Kimpton. "9½" x 6½", pp. 784, with 26 illustrations. Price: £5 5s.

THIS is the first appearance of this book, and therefore one wonders whether there is a place for yet another book. The reason is stated by the author in the preface—most books on toxicology are written by doctors and others not actively engaged in clinical practice. Dr. Locket, who is senior physician and officer-in-charge of the Barbiturate Unit at Oldchurch Hospital, Essex, is therefore a person well qualified to present this information to other practising doctors and undergraduates.

The book is in three parts; the first, comprising a little over 100 pages, discusses basic treatment in poisoning. This is a very practical section, dealing with immediate treatment and with the effects of various poisons on various systems. Thus gastro-intestinal irritation, respiratory failure, disorders of fluid and electrolytes, renal and liver damage, disturbances of the blood, and some antidotes are fully discussed, and the various treatments set out.

The second section deals with the symptoms and treatment of individual poisons, grouped chemically, and including poisonous plants and venomous animals. This section, which occupies about 450 pages, is very detailed, and one is hard pressed to discover a poisonous agent (including therapeutic agents) which does not receive a mention. There is even a chapter on radioactive substances and atomic bombs.

There is a short third section, which deals with the identification and estimation of common poisons and poisonous plants. Finally there are four indexes, covering treatment of individual poisons, authors mentioned in references, plant names, and subjects.

We are very impressed with this book. It fills a gap, and provides an excellent text-book for those especially interested in this subject, and at the same time a reference book for the occasion when one is confronted with a patient suffering from poisoning. On such occasions one is usually trying to rely on knowledge acquired in student days and not refreshed since, or one is completely ignorant. This book, and this book alone, will then serve a real need, and should not be far away.

Of criticism we have little. However, there is one major deficiency. One is confronted with a patient who has been spraying fruit trees, and does not feel well. Is this poisoning, and if so, what are the possible agents? This and many similar problems frequently come before the clinician. It has always been difficult to obtain information on the possible agents, let alone their clinical features and treatment. This book does not readily provide this starting point. There should be a section at least listing the ingredients of all toxic preparations used in industry, on the farm and orchard, in the home *et cetera*. The information in the book is very up to date; yet it is odd that on page 101 reference is made to modern work (1954) on the role of

the blood ammonia content in causing some of the clinical features of hepatic failure, although this is not applied on page 108, where the recommended diet (1946) for liver failure could be calculated to raise the blood ammonia level. There are a few, but very few, similar errors, which will no doubt be corrected in future editions. To these we shall look forward, as toxicology is always a "progressive" subject. We can therefore recommend this book to the undergraduate, the general practitioner and the consultant alike.

The Eye: In General Practice. By C. R. S. Jackson, M.A., B.M., B.Ch. (Oxon.), D.O.M.S., F.R.C.S. (Edin.); 1957. Edinburgh and London: E. and S. Livingstone, Limited. 8½" x 5½", pp. 160, with 25 illustrations. Price: 21s.

THIS small book (152 pages, 25 illustrations) has been written, as the author explains in the preface, with the special needs of the general practitioner in mind, and with three objects: (i) to describe the common diseases of the eye; (ii) to indicate the ways in which dangerous diseases of the eye may be recognized and to show the reasons for seeking specialist advice; (iii) to attempt to help the general practitioner in the interpretation of reports from the specialist.

The contents are divided into three parts; the first and longest describes the common diseases of the eye, the second section deals with the eye in diseases of other parts, and there are two brief chapters on administration in the United Kingdom.

The author has largely succeeded in his three objects, using for the main part brief, simple language and orthodox teaching.

The chapters on the watery eye and errors of refraction and ocular headache provide useful material for the general practitioner; but the book reaches its peak when concomitant squint is discussed. The cover test, which is so essential in diagnosis, and the urgency of specialized treatment, are forcefully and clearly described.

In the discussion of uveitis, the signs and symptoms are dealt with excellently; but one would have expected toxoplasmosis and brucellosis to be mentioned among the causes.

With regard to congenital cataract, the statement is made that "in the child, the need for treatment depends purely upon the visual defect"; this is true, but a general practitioner could not be expected to deduce from that bald statement the urgent need for early treatment of an infant with dense bilateral cataracts, to prevent nystagmus.

There are several other notable omissions and commissions, the chief being concerned with the treatment of glaucoma. Apparently the author does not believe that simple glaucoma should be treated medically as long as possible, whereas congestive glaucoma is a surgical problem as soon as it is diagnosed.

Alpha-globulin and steroids are used in the treatment of herpes zoster ophthalmicus in most countries, but are not mentioned; and the casual treatment of hyphema (including, be it noted, a mydriatic) cannot be condoned. Corneal grafting in the treatment of mustard gas keratitis is omitted.

To sum up, there is a need for such a book, and this one can be recommended; but we should like more recent trends to be mentioned, and perhaps both sides of controversial subjects could be stated (for example, the pros and cons of extracting a unilateral cataract), instead of the author's own view alone.

The Measurement of Body Radioactivity. Edited by C. B. Allsopp; 1957. London: British Institute of Radiology. 9½" x 7½", pp. 136, with illustrations and tables.

IN a period when quantitative information is urgently needed about the permissible levels of absorbed ionizing radiations in the human body, the publication of this seventh supplement of *The British Journal of Radiology* is welcomed. It records the proceedings of a conference considering the problems of "The Determination of the Natural Radioactivity of the Body and Methods of Determining the Smallest Possible Increase that may occur from Occupational or other Causes". Delegates attended from Denmark, Sweden, Germany, the United States, Canada, Australia and Great Britain.

The great majority of the papers are likely to be more easily intelligible to physicists than to physicians, as they are often concerned with the principles of the construction of the highly sensitive measuring instruments. High-pressure ionization chambers, large volume scintillation

counters, fluid or plastic, and large thallium-activated sodium iodide crystals are examples. The last-named would appear to have practical advantages in the estimation and identification of specific isotopes in the presence of the natural potassium activity.

Reference is made to the recognition of the presence in humans of a fission product ^{137}Cs "correlated with the amount of milk intake in the diet". The amounts of ^{137}Cs indicated suggest that the increase in the dose rate of "natural" radiation due to this element is still negligible compared with other sources, but already comparable to that of ^{14}C .

The measurement of human radium burdens—both the normal in different areas and the levels in some industrial and laboratory workers—is described in several papers. Of particular interest are the reports of the distribution of radium from a man concerned with radium and radon production for over thirty years. Five papers from English workers in several centres described microradiographs and autoradiographs, measurement of body γ ray emission, and breath measurements. Amongst the conclusions it was noted that: "Radium at the time of uptake, is deposited in areas of active bone growth, the concentration depending on the degree of activity; the persistence on how far resorption and remodelling occur."

The supplement is well illustrated, and has many tables of numerical values and many diagrams and graphs. This is a specialized study of an aspect of public health which in the twentieth century has become of first importance.

Operative Surgery. Under the general editorship of Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S.; Volume I, Introductory, Surgery of Trauma, Abdomen (Part); Volume II, Abdomen (Completion); 1956. London: Butterworth and Company (Publishers), Limited. 11" x 8½", pp. 795, with many illustrations. Price: £6 10s. per volume.

The progress of surgery has been such that it is no longer possible for one or two authors to present an authoritative book on operative surgery. Professor Charles Rob and Mr. Rodney Smith have acknowledged this, and "have called freely on a large and representative group of colleagues in the preparation of this series, of which the first two volumes are available for review. But they have done more: realizing the importance of the visual approach, they have made their volumes literally a series of illustrations qualified by a minimum of text. They have chosen well-recognized masters to write the many sections, and these surgeons have described the operations they favour rather than recording all the known operations. These innovations are highly commendable, and if the subsequent volumes maintain the standard of these samples, the completed work should be a source of pride to British surgery and should become indispensable to candidates for higher degrees and to those who practise surgery in centres large and small. Although the completed series will be large and expensive, it should prove a useful comfort to those men in the country who are occasionally obliged, because of their relative isolation, to perform some operations of which their experience is necessarily very limited. The publishers are to be congratulated on the production of volumes that are a credit to British workmanship. The general editing has been faithfully done and the illustrations are really splendid.

In these volumes, in which the standard is uniformly excellent, it is difficult to single out sections for special mention; but we were most impressed by the contributions of Tanner, Milnes Walker and Maingot. There is probably some good reason for the system adopted for numbering the pages, but it is a little confusing; there are, for example, three pages numbered 60 in Volume I. In this volume the name "Lotheissen" is misspelt, but the correct spelling appears in Volume II.

In Volume I an illustration depicts the use of an amputation knife for radical mastectomy; surely most modern surgeons prefer the scalpel for the careful raising of the skin flaps. The section on wound dehiscence does not emphasize the importance as causal agents of intra-abdominal sepsis, ileus, wound infection and hematoma. Reclosure in layers is rarely practicable and the attempt is often unwise; but if all-layer sutures are used, the results are satisfactory and incisional hernia should not be inevitable. Again, in a later section on wound closure in Part III, it is strange to see such scant reference to tension sutures in abdominal wounds, as their value is accepted by many surgeons, and in the same section to read that "there is some evidence that a peritoneal suture is unnecessary"; this will come as a shock to those who have always struggled to ensure a good peritoneal closure.

Modern advantages have made open methods of intestinal anastomosis generally safe; but there are still occasions when it is safer to employ one of the closed methods as described in Volume II by R. V. Cooke and also by D. M. Douglas. The former, at page 444, states that "as far as intestinal resection and anastomosis is concerned, the criticisms [i.e., of closed anastomosis] have been shown to be invalid", although earlier in Part III Ogilvie appears to despise such techniques. Ogilvie also appears to underrate the importance of peritoneal cover and the Lembert suture in intestinal anastomosis.

In the section on gastro-jejunostomy, it is a little disappointing to note the failure to stress the fact that the stoma should be at the most dependent part of the stomach—that is, on the greater curvature opposite the *incisura angularis*, and not on the posterior wall parallel to the greater curvature. To function well and give good results, the stoma should be placed in the stomach in a position analogous to the drain in a bath.

The section on hydatid disease is brief. The three-way syringe and formalin method is suitable only for univesicular cysts, and these are not common. When a transpleural approach is necessary, great care is required to prevent contamination of that cavity, and the adjacent layers should be sutured to prevent leakage. Calcified hydatid cysts do not call for any interference.

However, as the general authors state in the introduction, there will not be universal agreement on many details, and the work should be appraised as a whole; on this basis, it is only to be commended as a thoroughly good contribution to our surgical literature.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Human Blood Coagulation and its Disorders", by Rosemary Biggs, B.Sc. (Lond.), Ph.D. (Toronto), M.D. (Lond.), and R. G. Macfarlane, M.A. (Oxon.), M.D. (Lond.), F.R.S.; Second Edition; 1957. Oxford: Blackwell Scientific Publications. 8½" x 5½", pp. 504, with 53 illustrations. Price: 42s.

Much of this book has been rewritten since the first edition was published in 1953.

"Synopsis of Gastroenterology", by Rudolf Schindler, M.D., F.A.C.P.; 1957. New York and London: Grune and Stratton. 9" x 6", pp. 418. Price not stated.

"Written specifically for the general practitioner and the internist."

"The Clinical Management of Varicose Veins", by David Woolfolk Barrow, M.D.; Second Edition; 1957. New York: Hoeber-Harper. 9½" x 6½", pp. 192, with 70 illustrations. Price: \$6.00.

This book has been revised and enlarged since the first edition of 1948.

"Principles of Surgical Physiology", by Harry A. Davis, M.D., C.M., F.A.C.S.; 1957. New York: Paul B. Hoeber, Incorporated. 10" x 6½", pp. 864, with 49 illustrations. Price: \$20.00.

The author has attempted to organize those physiological facts and concepts which the surgeon needs in his daily work.

"Practical Office Gynecology", by Albert Decker, M.D., D.O.G., F.A.C.S., and Wayne H. Decker, M.D., D.O.G.; 1956. Philadelphia: F. A. Davis Company. Sydney: Angus and Robertson, Limited. 9½" x 6½", pp. 404, with 103 illustrations. Price: £5 15s. 6d.

Designed for the non-specialist.

"The Year Book of the Eye, Ear, Nose and Throat (1956-1957 Year Book Series)." "The Eye", edited by Derrick Vail, B.A., M.D., D.Oph. (Oxon.), F.A.C.S., F.R.C.S. (Hon.); "The Ear, Nose and Throat", edited by John R. Lindsay, M.D.; 1957. Chicago: The Year Book Publishers, Incorporated. 7½" x 5½", pp. 448, with 128 illustrations. Price: \$7.00.

One of the Practical Medicine Series of Year Books.

The Medical Journal of Australia

SATURDAY, JULY 27, 1957.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of the article. The abbreviations used for the titles of journals are those adopted by the *Quarterly Cumulative Index Medicus*. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

SMOKING AND LUNG CANCER.

THE death rate from cancer of the lung in Australia has been increasing steadily for many years. From an examination of the official statistics for Australia from 1908 to 1945, H. O. Lancaster¹ concluded that there had been no certain increase in the mortality from cancer in general over the period studied. On the other hand, reporting on a study of the mortality from cancers of the lung, Lancaster² stated that the male rates were about three times the female rates, and at every age there had been a steady increase in the rate since 1920. The rates for the period 1946 to 1948 were almost three times as great as the rates in the period 1911 to 1920. The Australian rates had not, however, attained the high levels holding in England and Wales. An examination of the most recent figures available shows that in the nine years from 1946 to 1955 the crude death rate from cancers other than respiratory has remained almost stationary, but the crude death rate from cancer of the respiratory system has jumped from 81 to 146 per million *per annum*, a rise of 80%. In a paper on the epidemiology of lung cancer published in 1955, Robert Fowler³ showed that the incidence of bronchial carcinoma in Australia was increasing at a uniform rate—7.7% *per annum* for males and 4.6% *per annum* for females. He gave reasons for the opinion that the increase was largely independent of improved methods

of diagnosis and of change in the age composition of the population. A significant part of the increase was attributed to "cumulative pathogenic forces" which were almost certainly environmental in origin. After referring to the rising tide of evidence from Britain and the United States of America which incriminated smoking as a lung cancer pathogen, Fowler expressed the view that the smoking habits of Australians were consistent with the theory that habitual heavy smoking was similarly blameworthy in Australia.

So much has now been written on the possible relationship between smoking and lung cancer that it would be foolish to attempt to review the literature here. Nor is it necessary at this stage. Most of our readers will have had the opportunity of reading for themselves the series of convincing studies on the subject by Richard Doll and A. Bradford Hill published in the *British Medical Journal* over the past five years; these include retrospective studies and, most recently, a prospective study based on the smoking habits of over 40,000 British doctors. Numerous reports on the same subject have come from other countries, and all with the same burden—that a persistent relationship exists between carcinoma of the lung and cigarette smoking, a relationship which appears beyond reasonable doubt to be causal. Now we have the statement just issued in Great Britain by the Medical Research Council.⁴ In this, reference is made to the rising death rate from lung cancer in Britain; it has more than doubled in the ten years from 1945 to 1955, and the trend appears not yet to have reached its peak. The increase is not regarded as being explained by improved diagnosis or increase in the number of older people in the population. Its extent and rapidity are stated to "point clearly to some potent environmental influence which has become prevalent in the past half-century and to which different countries, and presumably also men as compared with women, have been unequally exposed". Two main environmental factors are considered: the smoking of tobacco and atmospheric pollution. On the question of smoking, two types of evidence are examined: epidemiological surveys and laboratory evidence. The results of 19 retrospective inquiries (in Great Britain, the United States of America, Finland, Germany, Holland, Norway and Switzerland) are stated to agree in showing more smokers and fewer non-smokers among the patients with lung cancer and a steadily rising mortality as the amount of smoking increases. Two prospective inquiries, one in the United States of America covering 190,000 men aged fifty to sixty-nine years, and the other in Great Britain (Doll and Bradford Hill's study of 40,000 doctors already referred to), have produced results which are essentially the same. The British investigation has shown with regard to lung cancer in men: (i) a higher mortality in smokers than in non-smokers; (ii) a higher mortality in heavy smokers than in light smokers; (iii) a higher mortality in cigarette smokers than in pipe smokers; (iv) a higher mortality in those who continued to smoke than in those who gave it up. The death rate amongst heavy smokers who continued to smoke was nearly 40 times the rate among non-smokers. The evidence suggests that the proportion of lifelong heavy cigarette smokers who will die of lung cancer in Britain is of the order of 1 in 8; the figure for

¹ M. J. AUSTRALIA, 1950, 1: 501 (September 30).

² M. J. AUSTRALIA, 1953, 2: 355 (December 5).

³ M. J. AUSTRALIA, 1955, 1: 485 (April 2).

⁴ *Brit. M. J.*, 1957, 1: 1523 (June 29).

non-smokers would be of the order of 1 in 300. The Council's report points out the particular importance of the observation on the effect of giving up smoking, since "it indicates that men who cease to smoke, even in their early forties, may reduce their likelihood of developing the disease by at least one-half". The comment is added that the evidence is further strengthened "by the observation from several sources that the extent of the relationship with smoking differs for different types of lung tumour which can be distinguished only by microscopical examination"—a reference to the finding that the relationship appears to hold only for epidermoid and anaplastic cancers (including oat-cell cancer) and to apply to a less degree (if at all) to adenocarcinoma. The laboratory evidence shows that five substances have been found in tobacco smoke which can, in certain circumstances, cause cancer in animals, and that painting concentrated extracts of tobacco tar on the skin of animals has produced tumours. There is no certainty that the low concentrations of known carcinogens in tobacco smoke could be harmful to human beings, but "the finding of carcinogenic agents in tobacco smoke is an important step forward, in that it provides a rational basis for the hypothesis of causation". The question of the possible role of atmospheric pollution is considered in the report, and the following conclusion is reached: "On balance, it seems likely that atmospheric pollution plays some part in causing the disease, but a relatively minor one in comparison with cigarette smoking." Further reference to this last-mentioned question, leading to similar conclusions, will be found in a paper by E. L. Wynder,¹ which deals constructively with the whole problem of causation of lung cancer. The Medical Research Council report goes on to state that many factors other than tobacco smoking are undoubtedly capable of producing lung cancer; but so far no adequate explanation for the large increase in the incidence of the disease has been advanced save that cigarette smoking is indeed the principal factor in its causation.

There is no reason to doubt that these findings apply equally well in Australia as in Great Britain and elsewhere. It should be noted that 1334 persons (1128 men and 206 women) died of lung cancer in Australia in 1945, which represents an increase in mortality rate of over 80% in a decade. Less significant, but by no means negligible, is the steadily mounting evidence that tobacco plays a role in various other disabling and fatal diseases. Its effect on the heart has been reviewed by Paul W. Clough,² who concludes that for subjects with cardiac disability smoking is undesirable, apart from its effects on the respiratory tract, that it increases the load on the heart and involves some risk of injury that cannot now be assessed, and that there is a possibility but no proof that it may cause or accelerate degenerative changes in the myocardium or coronary arteries, as it probably does in the peripheral vessels. C. R. Lowe³ has produced evidence to suggest that smoking may be an important cause of the breakdown of healed or quiescent respiratory tuberculosis in adults, and may account for a considerable part of the excessive male mortality in middle and late life. In a brief paper which refers mainly to the pharma-

cological actions of nicotine, E. M. Vaughan Williams⁴ discusses its effect on the heart and blood-vessels and on the gastro-intestinal tract, especially in the presence of peptic ulcers; he brings forward reasons for regarding tobacco as harmful in several diseases, not only on the empirical grounds of the results of giving up smoking on therapy, but also on rational pharmacological grounds.

It is time, and more than time, to take these findings to heart. The British Government is apparently going to do something positive about it, and it is to be hoped that in this country both State and Federal Governments will realize the importance of the matter. The most useful line of approach appears to be a vigorous but informed and balanced campaign to encourage young people not to start smoking, and to persuade smokers to give it up or cut it down. The value of a deliberately restrictive programme is questionable. Australians generally do not take kindly to prohibitions, especially on a matter which may well be regarded as one for individual judgement and responsibility; more is likely to be achieved by a positive approach aimed at obtaining voluntary cooperation. Moreover, we certainly do not wish to cultivate hypochondriasis and cancerophobia. For some individuals it will probably be necessary, as Vaughan Williams states, to present the other side of the picture—that although 50 of every 1000 young adults who smoke may be expected to die of lung cancer, 950 will probably not die of lung cancer. Vaughan Williams goes on to comment:

We all have to die of something, and not everybody would approve a sense of values whose adherents deprived themselves of a lifetime of pleasure in order to improve their chances of shifting from one mortality group to another.

This again is an extreme point of view, with several generalizations that should be kept in perspective. It might be added that not everybody (perhaps hardly anybody, if he really thought about it) would elect to die of lung cancer. Not to prolong the dialectical argument, we would suggest that any campaign undertaken should be as simple, as positive and as reasonable as possible. The greatest opportunity for good in this matter probably lies in the hands of the practising members of the medical profession, who are in a position to know the facts and to influence their patients and others as individuals. A good example from them is likely to be particularly effective.

Current Comment.

PROTEIN DIGESTION AND ABSORPTION.

For many years it has been held that ingested proteins are broken down, in part, in the stomach, to proteoses and peptones, that the undigested protein with the proteoses and peptones passes to the small intestines, where they are broken down completely to amino acids by pancreatic and intestinal enzymes, and that the amino acids, as separated, are absorbed by simple diffusion through the intestinal mucosa. Recent investigations have shown that events are not as simple as this. It has been known for many years that some proteins can be absorbed from the intestine, to a greater or less degree, in an unaltered state. This cannot occur to any very great extent; but in infants,

¹ *Brit. M. J.*, 1957, 1:1 (January 5).

² *Ann. Int. Med.*, 1956, 45:319 (August).

³ *Brit. M. J.*, 1956, 2:1081 (November 10).

⁴ *M. Press*, 1957, 237:35 (January 9).

who normally absorb small amounts of unchanged egg albumin, the absorption may be increased fivefold during recovery from diarrhoea, and become an important factor in sensitizing the infant to egg albumin. Apart from such events a preponderance of evidence supports the view that food proteins normally are completely hydrolysed to their constituent amino acids prior to absorption. Recent investigations have shown that the absorption of amino acids is far from simple. E. S. Nasset¹ presented a paper on the subject at a symposium in Los Angeles in May, 1956, in which he reviewed the new conceptions which have developed over the past few years, many of them from his own laboratory. It has been demonstrated by several workers that amino acids are absorbed from the intestine at very different rates. Further, the absorption of a particular amino acid may be considerably altered in the presence of one or more other amino acids. Thus the presence of tryptophane greatly reduces the absorption of histidine, but the absorption of tryptophane is not affected by histidine. From a knowledge of the rate of absorption of single amino acids one cannot predict the rate of absorption of any amino acid in a mixture such as results from complete digestion of any protein. The differences in the rate of absorption could be interpreted to mean that differences in biological values of proteins might be caused by unequal supplies of essential amino acids at the site of synthesis.

In intravenous feeding all the essential amino acids must be injected simultaneously in order to obtain maximum effects. Thus, if rats are given tryptophane twelve hours after they have consumed a diet deficient in tryptophane, the result is ineffective.

Nasset and his co-workers gave dogs various test meals and killed them one and a half hours later for chemical examination of their digestive tracts. An egg albumin test meal was used as representing a complete protein of high biological value, and zein was used as an incomplete protein of low biological value. A non-protein diet consisting of sucrose and lard was also used. Some extraordinary results were obtained. The total nitrogen recovered from various parts of the small intestine remained constant in the normal animal regardless of the protein in the test meal. The amount of nitrogen ingested does not appreciably affect the amount of nitrogen recovered from the small intestine. Excess ingested protein is retained in the stomach and released gradually into the duodenum. The content of the different amino acids is very different in egg albumin and zein; but after test meals with one or other of these proteins the distribution of the amino acids in the contents of the jejunum is almost the same for the two proteins, and non-protein test meals give amino acid mixtures in the jejunum which can scarcely be distinguished from those derived from protein test meals. One must conclude that, whatever the protein in the test meal, there is a transfer of appreciable quantities of nitrogenous material into the lumen of the small intestine. The hydrolytic enzymes are proteins, the digestive juices also contain mucoproteins, and the intestinal mucosa is continually being desquamated. Apparently enough of these endogenous proteins passes into the small intestine to dilute the amino acid mixture sufficiently to obscure any amino acid peculiarly characteristic of a food protein. An amino acid analysis of the different enzymes which pass into the small intestine shows that they are very different in composition. Evidence is given to support the idea that, during the process of digestion, a great deal of endogenous protein is transferred into the lumen of the intestine, where it is hydrolysed and mixed with the amino acid of the ingested protein. This may be regarded as a homeostatic device that, within limits, assures the sites of protein synthesis a mixture of amino acids with minimal variation. The absorption from the small intestine seems to be of a mixture which remains relatively constant in composition. Nasset has estimated that 50 to 100 grammes of endogenous protein are transferred into the digestive tract of a human adult every day. As he comments: "In

a sense, therefore, all human beings are cannibals and the usual concept of vegetarianism is a myth."

These considerations do not affect the validity of the idea of essential amino acids and the concept of the biological value of dietary proteins. The homeostatic mechanism evens out temporary irregularities, but the deficiency of one or more essential amino acids or the addition of a single amino acid can upset the balance. This indicates a very real hazard in the fortification of foods with amino acids.

TENTH WORLD HEALTH ASSEMBLY.

THE World Health Organization has supplied details of the principal matters dealt with at the tenth World Health Assembly, which recently concluded a three-week session presided over by Dr. Sabih Hassan Al-Wahbi, former Minister of Health for Iraq. In the course of this session the Assembly defined the programme of work of the World Health Organization for 1958 to be financed by a budget of thirteen and a half million dollars, and took important decisions increasing the responsibilities of the World Health Organization in cancer research, malaria eradication, health statistics and field activities to assist more than 100 governments in developing their health services.

This Assembly was the first in eight years to be attended by four formerly inactive members: Albania, Bulgaria, Poland and the Union of Socialist Soviet Republics. At the end of the session Roumania also announced that it had resumed its active participation in the World Health Organization. The Assembly welcomed a new member State, Ghana, which had previously participated as an associate member (the Gold Coast). The Assembly decided to renew the contract of Dr. M. G. Candau, Director-General, at the expiration of his present term of office on July 21, 1958, and offered him a new contract for up to five years. Dr. Candau is to give his reply before November 1, 1957. Two distinguished scientists were honoured by the Assembly, which awarded the Léon Bernard Foundation Prize to Dr. Marcin Kacprzak, of Poland, in recognition of his outstanding contribution and practical achievements in the field of social medicine. Dr. Paul F. Russell (United States of America), of the Rockefeller Foundation, received from the hands of the President of the World Health Assembly the Darling Foundation medal and prize for outstanding achievements in the control of malaria. Another personality honoured by the Assembly was Dr. Ali T. Shousha, retiring Regional Director for the Eastern Mediterranean. He was praised as one of the pioneers of international health work, and the Assembly paid him tribute for his devotion and achievements in developing public health services in a vast region.

On the technical side, the 1958 programme of work as approved by the Assembly includes the implementation of almost 700 health projects in 112 countries and territories. The Assembly noted with satisfaction a considerable increase of health activities proposed for the African Region in the control of communicable diseases in rural areas. Other features of the approved programme include the development of the technical services that the World Health Organization renders to all countries alike in the fields of epidemiology and quarantine, health statistics, therapeutic substances, drug addiction and development of standards for public health laboratories. As regards disease control, the Assembly approved in particular increased activities to achieve malaria eradication: so far eradication has been achieved in 10 countries or territories, is under way in 15, and has been initiated or planned in 38. In order to support these activities the World Health Assembly called for increased contributions to the world malaria fund created two years ago, and asked that methods of fund-raising be utilized other than inviting contributions from governments. Delegates attached particular importance to the World Health Organization's

¹ J.A.M.A., May 11, 1957.

programme dealing with health aspects of the peaceful uses of atomic energy. This programme lays emphasis on the training of health physicists and medical personnel. An Indian proposal that the Assembly should appeal for a ban on atomic bomb tests was ruled out of order because the subject had not been included on the agenda. The Assembly decided that the World Health Organization should undertake an important research programme on the epidemiology of cancer, in the belief that a comparative study of the variations between cancer types in different countries would yield a clue to the origin of this disease.

After a long debate, the Committee on Administration, Finance and Legal Matters rejected a proposal, put forward by the Canadian delegation, for the setting up of a budget working group in future Assemblies to make a close scrutiny of the programme and budget of the Organization. Another proposal from the United States of America delegation that the adoption of the annual budget of the World Health Organization should require a two-thirds majority, as is the case for certain important decisions, was also rejected by the Committee on Administration, Finance and Legal Matters. As usual the Assembly devoted two days to technical discussions. This year's subject was the role of the hospital in the public health programme. Next year the World Health Assembly will meet in the United States, where it will also hold a special session to celebrate the tenth anniversary of the World Health Organization.

UNCONSCIOUS MOTIVES OF WAR.

THE psycho-analytical viewpoint on factors leading to warfare has been outlined in a recent book by Alex Strachey,¹ who on his opening page reminds us that the atom bomb has ushered in a new era: a couple of thousand might destroy mankind, and a single cobalt bomb could mean annihilation. In such a setting, discussion on the causes of war are not merely opportune but vital. Strachey points out that war has persisted through the centuries and is not confined to any individual racial group. His search for causation is outlined in a section on the undercurrents of individual psychology. The concepts outlined by Sigmund Freud are freely used. A description of libidinal energy or *libido* and the instincts introduces the concept of ambivalence, wherein love and hate are reversible. Displacement is illustrated by the example of a man who wanted to kick his aunt downstairs, but became possessed with a desire to kick her dog instead. As a result of such unconscious happenings, it would seem that the alleged causes of war might also differ from reality.

Subsequent chapters outline the classical features of Freudian psychology and include discussions on the ego and its defences, distortions in projection and introjection, origins of moral sense, infantile stages of development, Oedipus phases and regression. Importantly space is devoted to danger points in group psychology. Strachey argues that the group is a regressive force. Rank and file follow a leader with autocratic power. Inhibitory capacities are lessened, and violence can result as in *Julius Caesar* (Act III, Scene III):

2nd Citizen. Tear him to pieces; he's a conspirator.

Cinna. I am Cinna the poet, I am Cinna the poet.

4th Citizen. Tear him for his bad verses, tear him for his bad verses.

Cinna. I am not Cinna the conspirator.

2nd Citizen. It is no matter, his name's Cinna; pluck but his name out of his heart, and turn him going.

Of late years destructive influences of this pattern have been so rampant that the reader is tempted to skip the pages, hoping to find that a psychological remedy has been given to us by the author. His suggestion is that as "the chief villain of the piece seems to be the National

State in its aspect as a regressive group", our first aim should be to whittle its strength. Democratic government must be fostered. Potential Caesars, Cromwells, Hitlers and Mussolinis must be kept down. Admittedly leaders are necessary, but steps must be taken to limit their powers. A further method of loosening the State bonds is to strengthen the power of non-aligned groups. Among these are the churches, local government groups and presumably social welfare organizations. Local separation of racial groups, as in the Swiss cantons, is desirable. Foreign travel must be encouraged. International organizations, such as Red Cross and Boy Scouts, have a favourable influence and should be fostered.

Strachey regards it as equally important for us to pay attention to the small family group and the individual. Child guidance should be so planned that the acquisitive and destructive instinctual trends are mitigated. Wise parenthood and nursery schools must be encouraged. Lastly, as it has been shown that hostile and antisocial traits in individuals can be diverted by psychoanalysis into better channels, it is considered that publicity must be given not merely to the truths of psychology but also to the possibilities of treatment. However, the first most urgent task of statesmen and scientists is seen as the dissemination of knowledge concerning the extent of the threat of extermination which faces us.

STARCH GRANULOMATA.

For many years before the second World War talc was in almost ubiquitous use as a glove lubricant. Between 1933 and 1941 there was a growing number of publications which drew attention to the irritative properties of talc. Not a few patients complaining of abdominal symptoms underwent laparotomy, only for the surgeon concerned to find granulomatous and chronic inflammatory lesions, at the centre of which were nidi of talc. It was subsequently shown that talc as a glove lubricant was responsible for such lesions, and that they had developed at a previous operation, at which glove powder had inadvertently been introduced. The possible methods of implantation in probable order of importance were unwashed gloves, perforated gloves, talc spilled onto instruments and sutures, and airborne particles.

As a result of these observations it became obvious that talc was unsuitable as a glove lubricant and that alternatives were required. Extensive experimental work mainly upon dogs and rabbits showed that starch was a suitable substance and produced only minimal tissue reactions. Within recent years many hospitals have taken to starch preparations as a glove lubricant. The Jessop Hospital for Women, Sheffield, England, is one such hospital which began using starch in 1952. Since 1952 starch-containing lesions have been found at laparotomy on three occasions. None of the three patients had previously been operated upon. All had undergone a pelvic examination a few days before operation. All had a granulomatous mass, albeit of small size, either on the peritoneum or on an ovary, in addition to the pathological lesions for which they had been admitted to hospital. These granulomatous masses were found to contain starch granules at the centre.

The recognition of starch particles in sections was to a great extent accomplished by the use of polarized light. Comparisons were made between the appearance of starch on the lesions, that of the glove powder in common use, and that of samples of the commonly available starch powders, potato, maize, rice and wheat. There was a considerable variation in size and shape of starch particles from different sources, but also a wide variation in the individual starches. All the starches examined showed a Maltese cross configuration with polarized light. The best method of identifying the source of starch was by determining the total range of particle size and the mean diameter of particles. The particle size of the starch in the lesions corresponded most closely to maize starch and to the glove powder which, according to manufacturers,

¹"The Unconscious Motives of War: A Psycho-Analytical Contribution", by Alex Strachey; 1957. London: George Allen and Unwin, Limited. 8½" x 5½", pp. 288. Price: 25s.

was made from maize starch. None of the particles in the lesions corresponded to the peculiar oval shape of potato starch, and they were larger than the particles of the other common sources of starch. It was a reasonable assumption that the lesions had occurred as a response to the introduction of glove powder containing maize starch.

As the patients had had no previous operations, and as starch is cleared rapidly from the peritoneum by enzymatic action from polymorphonuclear leucocytes, it would seem that the starch was introduced to the peritoneal cavity by migration following a pelvic examination. C. P. Paine and P. Smith,¹ who investigated the cases in Sheffield, therefore made a search of the literature of talc granulomata, and found six cases in which no previous laparotomy had been performed. The six patients concerned, in many out-patient attendances, had undergone repeated vaginal examination. It would seem that careful removal of glove powder from gloves is required before pelvic examinations as well as before surgical operations.

REVERSIBLE METASTATIC CALCIFICATION (MILK DRINKER'S SYNDROME).

In 1949 C. H. Burnett and others² described a syndrome following prolonged intake of excessive quantities of milk and alkali, as may happen in those undergoing treatment for a duodenal ulcer. The essential features were hypercalcaemia without hypercalcuria or hypophosphatemia, calcinosis manifested by band keratitis, renal insufficiency with azotemia and mild alkalosis, and improvement following the adoption of a diet low in its content of milk and absorbable alkali. E. G. McQueen³ has pointed out that the development of this syndrome may not be possible in the absence of renal disease. Moreover, long-continued and excessive consumption of alkalis may also be a prerequisite in the development of the syndrome and may possibly be responsible for initiating the renal damage. So, despite the popular name of milk drinker's syndrome, which the condition has acquired, there is no implication that milk is *per se* harmful, especially in other than enormous quantities; perhaps, indeed, it would be better if the more prosaic alternative name of reversible metastatic calcification was generally adopted.

The diagnosis of this condition is indicated, according to M. H. Poppel and B. E. Zeitel,⁴ by the radiological finding of calcinosis in the presence of a history of prolonged and excessive milk consumption (usually for peptic ulcer) and renal insufficiency. The characteristic radiological appearance of metastatic calcinosis is one of calcific deposits in the subcutaneous tissues, usually in proximity to joints. The masses are amorphous; they vary in size from nodules to bulky tumours, and are unaccompanied by change in osseous structure. Ancillary findings include widespread calcifications in blood vessels, *falx cerebri*, kidneys and lungs. Poppel and Zeitel believe that conflicting theories of the pathogenesis of calcinosis in this syndrome can be unified into one concept. The *sine qua non* is prolonged excessive consumption of milk. The blood becomes saturated with calcium and phosphorus, which are precipitated in the renal tubules and parenchyma. If alkalosis is present, the kidneys excrete an increased quantity of acid. As a result, the rate of precipitation of calcium salts in the kidney is increased. Once renal insufficiency supervenes, excretion of calcium tends to be fixed, and the serum levels of both cations remain elevated. Metastatic calcinosis and further nephrocalcinosis result, with perpetuation of the cycle. Elimination of milk from the diet can bring about a return of serum calcium and phosphorus levels to normal and can reverse metastatic calcinosis, but cannot significantly reverse renal insufficiency. When metabolic acidosis develops in the course of uraemia, calcinosis progresses so

long as milk consumption continues. In the medical management of peptic ulcer, therefore, periodic determinations of serum calcium content, non-protein nitrogen content and carbon dioxide combining power are advisable. If the findings are abnormal, elimination of milk and absorbable alkali from the treatment regime is indicated.

THE DIFFERENTIAL DIAGNOSIS OF MALIGNANT MELANOMATA.

THE malignant melanoma remains one of the forms of neoplasia for which little can be done. In addition, it is notoriously difficult to decide whether any suspected lesion is in fact a malignant melanoma. H. Beerman *et alii*,¹ in their review of some recent literature on this subject, give a list of conditions to be considered in the differential diagnosis. This includes the following: pigmented nevus, sebaceous wart, *granuloma pyogenicum*, pigmented basal-cell carcinoma, histiocytoma, blue nevus, *verruca vulgaris*, fibroma, sebaceous cyst, keratoacanthoma, glomus tumour, and Kaposi's sarcoma. Beerman *et alii* also refer, almost as a footnote, to cutaneous and subcutaneous haemorrhage simulating a malignant melanoma.

Confusion between malignant melanomata and haematomata may seem unlikely; but confusion is often caused by the lack of a history of trauma with the haematoma on the one hand, and by the patient's insistence upon trauma as the exciting cause of a malignant melanoma on the other. R. H. Cowdell² has reported five cases of haematomata which simulated malignant melanomata, with the particular intention of obviating the otherwise necessary mutilating surgery. This group comprises five cases of haematoma occurring without a history of trauma. The lesions were of years' standing, and some even had a period when they enlarged rapidly. One patient had a subungual black spot which enlarged over a period of a few years, but which turned out to be a haematoma.

There seems little doubt that cutaneous and subcutaneous haematomata should always be considered in the differential diagnosis of malignant melanomata.

EMBRYO-LIKE BODIES IN TERATOMA TESTIS.

SMALL BODIES in testicular teratomata which are morphologically similar to the early developmental stages of mammalian embryos have been described from time to time, but only rarely. Very occasionally indeed the similarity between the embryos and the tumour bodies is extremely close. Such an instance has recently been described by R. Winston Evans.³ A testicular teratoma which had been noticed for six months was removed from a forty-one-year-old patient. Five years later he was alive and well with no clinical recurrence.

Histologically, apart from several embryo-like structures, there were areas of cartilage, smooth muscle, epithelial tubules, glandular components, pilosebaceous units, cornifying structures, and primordia of enamel organs. Several embryoid structures were found which mimicked closely the amniotic cavity, embryonic disk, intra-embryonic mesoderm and yolk sac, and gut endoderm of a normal presumptive human embryo. Occasionally a type of body stalk was observed, near which structures resembling cytotrophoblast and syncytiotrophoblast could be seen.

Embryoid bodies of various stages of development were found, but as the minimum age for the teratoma was six months and as the oldest embryoid bodies comparable morphologically would correspond to eighteen days, a continuous sequence of formation and disappearance may be assumed. Evans suggests that transplantation of pieces of similar tumours to male and female rats, in order to study the possibilities of further development of these embryoid bodies, would be of great value.

¹ *J. Clin. Path.*, February, 1957.

² *New England J. Med.*, May 19, 1949.

³ *Lancet*, July 12, 1952.

⁴ *Radiology*, August, 1956.

¹ *Am. J. M. Sc.*, April, 1955.

² *Brit. J. Surg.*, January, 1957.

³ *J. Clin. Path.*, February, 1957.

Abstracts from Medical Literature.

MEDICINE.

Dornase Aerosol in Bronchial Disease.

E. E. CLIFFTON (*Dis. Chest*, October, 1956) describes the use of an aerosol containing pancreatic desoxyribonuclease (dornase) in the investigation and treatment of bronchial disease. The contents of a vial of 100,000 units of dornase are dissolved in two to five millilitres of a sterile diluent and administered by means of an aerosol inhaler, oxygen being used for nebulization. When the enzyme is inhaled immediately before bronchoscopy, cytological examination of bronchial washings for evidence of carcinoma may be made more efficiently. No harmful complication has been encountered. The inhalation has given prompt benefit in the treatment of pulmonary deflation caused by mucoid bronchial impaction and of troubles arising from thick, tenacious sputum.

Lung Cancer Survivors.

R. H. OVERHOLT AND J. A. BOUGAS (*J. Thoracic Surg.*, October, 1956) have sought amongst 107 persons, who have survived the excision of proved lung cancer by more than three years, for common factors which might have had some bearing upon the capacity to survive. No common factors were found in the study of tumour and host characteristics. The few common denominators all pertained to case management: all survivors had had X-ray films revealing abnormal areas of density in the chest; all required surgical exploration to determine the true nature of the lesion throwing the shadow; and all were treated by excision of the cancerous lung. The authors hold that further improvement in the salvage of victims depends on three steps—discovery (X-ray examination), verification (exploration) and therapy (excision).

Triethylene Thiophosphoramide.

B. J. LEONARD *et alii* (*Lancet*, November 17, 1956) describe the treatment of Hodgkin's granuloma, chronic lymphatic leukaemia, polycythemia vera and other reticuloses with triethylene thiophosphoramide (thio-T.E.P.A.), a nitrogen mustard. The substance was dissolved in normal saline, 10 milligrammes per millilitre. Stored at 0 to 4°C., it remained potent for two or three months. A dose of 25 milligrammes was given intramuscularly, followed by further injections of 25 or 50 milligrammes if there were no bad effects. Most patients were ambulant out-patients. Nausea, vomiting and anorexia were noted in 7% to 31% of patients. In chronic lymphatic leukaemia six patients showed improvement, but caution was needed, because two patients with platelet counts below 100,000 per cubic millimetre died of purpura eighteen days after treatment was stopped. In lymphoid reticulosis, follicular reticulosis and reticulum-cell reticulosis, diminution in size of lymph glands and spleen lasted for some months. In Hodgkin's

granuloma, good effects were obtained when superficial glands were enlarged, but not when internal glands were enlarged.

Respiratory Recovery in Severe Poliomyelitis.

J. E. AFFELDT, A. G. BOWER, C. W. DAIL AND N. N. ARATA (*Arch. Phys. Med.*, May, 1957) have made a two-years' follow-up study of 500 respirator patients suffering from poliomyelitis, to determine the prognosis for such patients. The two-year mortality rate was 14%; 73% of patients became completely free of all respiratory equipment, and 13% still required some form of respirator equipment full-time or part-time two years after the onset. Over 50% of the deaths occurred in the first two weeks. The mortality rate decreased significantly from year to year; this indicated improvement in the treatment programme. Of the patients who became free of the respirator, 83% did so within six months of the onset.

Capillary Resistance in Poliomyelitis Patients.

H. N. NEU, M. S. KRAMAR AND W. ANTHONY (*Arch. Phys. Med.*, May, 1957) have studied the individual capillary resistance in 49 patients at the Poliomyelitis Rehabilitation Centre in Omaha, and the results were compared with those obtained by Kramar and others on healthy volunteers. The patients were divided into two groups: 1953-1954 (Group I) and 1955 (Group II). The members of Group II participated in a much more intensive rehabilitation programme than those of Group I, because of the development of the rehabilitation centre. The individual capillary resistance level was low in Group I and high in Group II. In both groups the fluctuations around this level were greater than in the healthy controls. Both the immediate and late types of capillary stress response were studied in 31 patients, ultra-violet light being used as a standard stress. No difference was found in the patterns of response or in their distribution between poliomyelitis patients and controls; yet a lower threshold of responsiveness to this stress may be postulated in the patient group. Five modalities of physical therapy were studied and compared in 26 patients. The immediate capillary response served as a yardstick. It was borne out that the stimulating effect of physical exercise was greatly augmented by a combination with some of the commonly used physiotherapeutic adjuncts.

Lente Insulin.

A. G. SPENCER AND M. E. MORGANS (*Lancet*, November 17, 1956) discuss the use of lente insulin. Two hundred patients were treated; 102 had been on protamine zinc insulin alone or with ordinary insulin. With lente insulin the diet was changed to give substantial snacks at 11 a.m. and 10 p.m. The insulin mixture was 30% insulin zinc suspension amorphous (semilente) and 70% insulin zinc suspension crystalline (ultralente), given in a single injection one hour before breakfast. The starting dose was equal to the total previous

insulin dose less 10%. The sugar content of the urine was tested twice daily and the blood sugar content occasionally. The control of the diabetes was satisfactory in 83%, 36% of the patients being improved, 47% unchanged and 17% worse. Patients with mild and severe diabetes were often better on their old insulin. Hypoglycæmic attacks occurred in 52% of patients on lente insulin. In general, the results of treatment with lente insulin were said to be satisfactory in spite of skin reactions, a 50% incidence of hypoglycæmic attacks and other complications.

Diabetes.

M. JERSILD (*Lancet*, November 17, 1956) discusses the use of insulin zinc suspension (lente) in diabetes. Generally, a diet of 2000 Calories was allowed (carbohydrate 200 grammes, fat 93 grammes and protein 87 grammes). One thousand patients were controlled on insulin zinc suspension. Of these patients, 90% were controlled by insulin zinc suspension, with an average dose of 40 units. Insulin zinc suspension (lente) was given alone in 74% of patients, insulin zinc suspension (lente) with amorphous insulin zinc suspension in 12%, and insulin zinc suspension (lente) with crystalline insulin zinc suspension in 8%. Local reactions were rare. The conclusion was reached that lente insulins controlled diabetes in most cases.

Electrocardiographic Leads.

A. I. SCHAEFFER *et alii* (*Am. Heart J.*, November, 1956) give reasons for supposing that the electrocardiograph leads II, III, aVR and aVL are superfluous, and that leads I and aVF contribute all the significant information that may be elicited from limb leads.

Adenovirus Vaccine.

M. R. HILLEMANN *et alii* (*J.A.M.A.*, January 5, 1957) describe an adenovirus (RI-APC-ARD) vaccine for prevention of acute respiratory illness. The virus was obtained from patients' throat washings. The method of preparation of the vaccine is described. Formalin was used to destroy the infectivity of the virus. Volunteers were inoculated with one, two or three injections. They all developed neutralizing antibody, sustained for at least sixteen weeks. Next, 25 volunteers were given one or two injections of vaccine, with the result that antibody developed in equal titres with one or two doses. A field evaluation was then made; 1200 newly recruited soldiers were given one millilitre of vaccine or a placebo, and a second dose six to nine days afterwards. Results showed that the vaccine was effective in preventing adenovirus one week after the initial injection, causing a marked reduction in the incidence during the second and until the fifth week after vaccination. Only one case of serologically proved adenovirus disease requiring the patient's admission to hospital occurred among 311 vaccinated recruits, in contrast to 61 cases among 313 controls from the same companies of soldiers. Non-adenovirus diseases such as influenza and streptococcal infections did not occur during the study period to

the end of the fourth week. Adenovirus (RI-APC-ARD) is the cause of an acute upper respiratory illness which is to be differentiated from the common cold and from influenza. The formalin-killed vaccine described is of value in the prevention of this adenovirus disease in a military population, but its role in civilian populations remains to be determined. In this investigation the duration of protection against the illness was not proved beyond the fifth week after vaccination.

Vasoconstrictive Effects of Tobacco Smoke.

J. W. ACKSTEIN *et alii* (*Am. Heart J.*, March, 1957) found in 28 out of 31 experiments with medical graduates that smoking two cigarettes resulted in reduction in the flow of blood in the foot by an average of 22%. The range was from 9% to 55%. There was no significant difference in the range or in the average values when the temperature of the room was lowered from 83° to 68° F. or when the subjects had abstained from smoking for one or two days previously.

Congenital Heart Defects following Maternal Rubella.

D. STUCKEY (*Brit. Heart J.*, October, 1956) points out that though there has been abundant confirmation of Gregg's observation that congenital heart defects may occur in children whose mothers have suffered from rubella during pregnancy, there is little detailed information available about the particular types of congenital heart disease that may occur. A survey of 27 children showed a wide variety of congenital heart defects; but in 13 the defect was a patent ductus arteriosus. Patent ductus arteriosus occurred about eight times more frequently than other forms of congenital heart disease compared with the normal relative incidence in the general population. It is suggested that the reason is that the cardiac septa, the main vessels and their valves are susceptible to damage by environmental factors for only a short period of some four or five weeks, whereas the ductus arteriosus is at risk for many months.

High Blood Pressure and Personality.

B. L. KALIS *et alii* (*Am. Heart J.*, April, 1957) used the techniques of psychodrama to observe 36 women, 14 with essential hypertension and 22 normal controls, under conditions of mental stress. The stress was induced by staging difficult situations, the subject being assigned a role and given the synopsis of an incomplete plot, which she was asked to act out with a professional actress. The actress skillfully involved the subjects in the interactions, highlighted the conflicts and, when necessary, pressed for resolution of the problem. Both blood pressure and heart rate, as well as psychical response to stress, differed for the two groups of women. The hypertensive women had poorer control of their emotions and behaviour, were less flexible and adaptive in situations of stress, and lacked appropriate assertiveness. These findings were consistent with those found in studies of "pre-hypertensive" college women. The authors suggest that pre-hypertensive as well as hypertensive

subjects perceive stress more readily and handle it less well than normal subjects.

The Dilemma of the Non-Toxic Nodular Goitre.

W. R. SCHILLHAMMER AND R. I. CRONE (*Ann. Int. Med.*, September, 1956) discuss the dilemma of the non-toxic nodular goitre, and inferences are drawn from the study of a series of 165 cases of non-toxic nodular goitre and carcinoma of the thyroid. The frequency of carcinoma in nodular goitre is probably far lower than has been reported, and the manner of selection of cases is largely responsible for the false picture currently depicting the frequency of carcinoma of the thyroid in non-toxic nodular goitre. If the patient has symptoms, he is more likely to have cancer when he is first examined. Though it seems likely that carcinoma is more prevalent in those glands containing a solitary nodule (from surgical material), the physician's inaccuracy in detecting the number of nodules present in a given gland makes sole dependency upon such an observation unreliable. Perhaps the use of radioactive iodine will be of assistance in the differentiation of carcinomatous and benign nodules of the thyroid. Until further long-term study clarifies this problem, it would seem appropriate to recommend operation in most cases of non-toxic nodular goitre.

Anæsthesia for Surgery of the Nose, Pharynx, Larynx and Trachea.

D. C. MOORE AND J. F. TOLAN (*Arch. Otolaryng.*, October, 1956) discuss the reasons why severe or fatal toxic reactions occur more frequently after topical application than after infiltration or nerve blocks. They state that a true allergy to local anæsthetic agents is extremely rare. At least two factors influence the severity of a high blood-level type of reaction. The first is the rate of absorption. Secondly, the severity of reaction varies according to the organs first supplied by the high concentrations of the drug-laden blood. In regional block injection methods absorption is relatively slow, and further retardation is able to be achieved by adding adrenaline. Dilution by the blood and detoxication by the liver keep pace with the rate of absorption, so that an extremely high blood concentration of the drug seldom reaches the heart and brain. On the other hand, topical applications of a local anæsthetic to the mucous membranes of the respiratory tract results in rapid absorption, especially if the drug reaches the single-cell epithelial layer of the pulmonary alveoli. It has been estimated that in this manner the blood level obtained may be equivalent to that following intravenous injection of a similar amount of the drug, and a high blood level of the drug may reach the heart and brain. Precautions may be taken to reduce the incidence of severe toxic reactions. Less of the drug should be given to patients of poor physical status. Solutions should be much more diluted for use in the mouth, pharynx, larynx and trachea. Premedication with barbiturates acts as prophylaxis against systemic toxic reactions. Chlorpromazine ("Largactil"), 25 milligrammes, given intravenously half an hour before opera-

tion has been found to be helpful. Emergency equipment should include a source of oxygen, to which a bag and mask are connected; so that, should respiration cease, artificial aeration may be carried on. Laryngeal tubes, laryngoscopes and bronchoscopes should be at hand. Suction apparatus and equipment for intravenous infusion of 5% dextrose solution should be available to provide a means of administering drugs intravenously. Ampoules of vasoconstrictor drugs to treat hypotension, and thiopentone solution for intravenous injection to control convulsions must be ready for use. Severe toxic reactions usually start with a faint giddy feeling. The speech may become incoherent, and unconsciousness and apnoea may ensue. Twitchings of the fingers and generalized convulsions may occur. Oxygen should be given by mask and bag immediately. Artificial respiration may be necessary. A fall in blood pressure should be countered with intravenous dextrose infusion and appropriate vasoconstrictor drugs. If convulsions persist, thiopentone should be given (0.6% solution intravenously or 2.5% solution from a syringe); 50 to 100 milligrammes of thiopentone usually will reduce the severity of convulsions. Rarely will more than 100 to 300 milligrammes need to be exceeded. It is wise with thiopentone to be prepared for intubation, as laryngospasm may occur. When laryngospasm does occur 20 to 40 milligrammes of succinylcholine given intravenously will often help to relax laryngospasm. It may also produce apnoea, so that further artificial respiration may be needed.

Chronic Toxicity of Ozone.

S. MITTLER, M. KING AND B. BURKHARDT (*Arch. Indust. Health*, March, 1957) showed that repeated exposures to 2.4 parts per million of ozone induced some hemorrhage and edema in lungs of rats. Adaptation to ozone was noted after thirty-two hours of accumulative exposure. Of 102 mice, 20% died after a continual exposure to 2.4 parts per million of ozone for 241 hours. Chronic exposure to ozone decreased the weight gain by young rats, and concentrations greater than 1.2 parts per million and longer than seven hours per day significantly affected the growth of young rats. Ozone did not reach or react with the blood of chronically exposed animals. There was no change in hematocrit or hemoglobin values.

Evaluation of the Hazards of Ozone and Oxides of Nitrogen.

H. E. STOKINGER (*Arch. Indust. Health*, March, 1957) presents evidence that ozone is a highly poisonous substance to laboratory animals. No experimental evidence was found that this toxicity is modified to a significant degree by the presence of nitrogen oxides that may accompany ozone production. The author states that any one of seven factors may modify the toxicity of ozone. Of these, youth, physical exertion, alcohol and respiratory infection tend to augment the injurious response or act to the detriment of the host; the remainder, intermittent exposure, premedication and preexposure, either reduce or eliminate the injurious effects of ozone.

Medical Societies.

THE MEDICAL SCIENCES CLUB OF SOUTH AUSTRALIA.

A MEETING of the Medical Sciences Club of South Australia was held on May 3, 1957, at the Anatomy Department, Medical School, University of Adelaide.

The Pathogenesis of Mouse Ascites Tumours.

P. WARNER read a paper on mouse ascites tumours. He said that transplantable mouse ascites tumours were those which, after intraperitoneal inoculation, caused the accumulation of fluid containing cancer cells in, usually, a monodisperse suspension. A prevalent suggestion was that the tumour cells multiplied while freely suspended in peritoneal fluid in a manner analogous to that of a bacterial culture. However, by the use of the sarcoma 37 ascites tumour, he presented evidence that the probable sequence of events was that, after inoculation, tumour cells settled in fatty tissue close to blood vessels from which they obtained nutriment for multiplication. The tumour growth occurring at that site interfered with the blood vessels constituting the radicles of the portal system, causing peripancreatic oedema. The oedema fluid passed into the peritoneal cavity producing the ascites, and the increasing number of cells suspended in the fluid were produced by desquamation from the growth foci within the tissues. Thus, from his observations, he believed that cells of ascites tumours multiplied within tissues and probably not at all in suspension in peritoneal fluid.

The Role of Sodium in Plant Nutrition.

P. F. BROWNELL discussed the role of sodium in plant nutrition, and described experiments in which sodium was shown to be an essential micronutrient for *Atriplex vesicaria*.

Plants were grown in a temperature-controlled cabinet with walls of polyvinyl chloride sheeting. That was supplied continuously with filtered air, which maintained a slightly positive pressure, and prevented the entry of dust. Nutrient salts were carefully purified by many recrystallizations in silica beakers, water was twice distilled in tinned metal stills and once in a silica still, and plants were grown in polythene vessels with "Perspex" tops.

When twenty-five days old, plants which had not received sodium sulphate could be distinguished from those which had received 0.2 milliequivalent per litre of sodium sulphate by their yellow colour and fewer leaves of smaller area. Necrotic areas, white in colour, appeared along tips and margins of cotyledons and older leaves on the thirtieth day, and plants began to die by the thirty-fourth day. Plants which had received 0.6 milliequivalent per litre of potassium sulphate in their cultures were indistinguishable from those which had not received sodium sulphate.

Another experiment showed that a delayed treatment with 0.1 milliequivalent per litre of sodium sulphate brought about complete recovery within a week when applied to the cultures of plants which had developed severe sodium deficiency symptoms.

It was further shown, that of the Group I elements examined—*vis.*, lithium, sodium, potassium and rubidium—only sodium was able to bring about recovery in sodium-deficient plants. Plants which received lithium, potassium or rubidium could not be distinguished from those which received no sodium.

THE CARDIAC SOCIETY OF AUSTRALIA AND NEW ZEALAND.

THE annual general meeting of the Cardiac Society of Australia and New Zealand (formerly the Australasian Cardiac Society) was held in Brisbane on May 27 and 28, 1957.

The following office-bearers were elected: *President*, Dr. J. Kempson Maddox; *Chairman*, Dr. Ellis Murphy; *Chairman-Elect*, Dr. John H. Halliday; *Honorary Secretary and Treasurer*, Dr. James M. Gardiner; *Members of Council*, Dr. C. R. Burns (New Zealand), Dr. Cyril Fortune, Dr. E. F. Gartrell, Dr. H. B. Kay, Dr. E. H. Roche (New Zealand) and Professor F. H. Smirk (New Zealand).

The President reported on the Organizational Conference of the Asian-Pacific Society of Cardiology, which was held in Manila in 1956. It has been decided that the next Congress of this Society will be held in Melbourne in 1960.

Further details of the Third World Congress of Cardiology have been received by the Honorary Secretary. This Congress is to be held in Brussels from September 14 to 21, 1958.

At the commencement of the scientific sessions, the President gave an address on the life and influence of William Harvey, the tercentenary of whose death is being celebrated this year. The following papers were presented at the scientific sessions: "Chronic Irreversible Beriberi Heart Disease", Dr. R. B. Blacket; "Left Ventricular Hypertrophy: Its Definition and Measurement", Dr. J. M. McPhie; "Kinking of the Aortic Arch", Bernard F. Vaughan (introduced) and Dr. C. Fortune; "Oxygen Diffusion at the Blood Gas Interface: A New Method of Appraisal", Dr. K. L. Cotton (introduced); "Pulmonary Compliance in Mitral Stenosis", Dr. B. C. Sinclair-Smith; "The Exercise Test in Doubtful Cases of Angina", Dr. Ralph Wishaw; "A Case of Acquired Wolff-Parkinson-White Syndrome", Dr. E. H. Roche; "The Familial Factor in Congenital Heart Disease", Dr. C. Fortune; "Phonocardiography in the Diagnosis of Congenital Heart Disease", Dr. James M. Gardiner; "A Radioactive Isotope Method of Estimating Cardiac Output", Dr. E. P. George, Dr. J. B. Hickie (introduced) and Dr. W. A. Seldon; "Absence of the Left Pulmonary Artery", Dr. E. J. Halliday; "The Use of the Pump-Oxygenator in Open-Heart Surgery", Mr. Kenneth N. Morris. A demonstration of clinical cases was arranged by Dr. Ellis Murphy and Dr. Harry G. Wilson.

The 1958 annual meeting of the Society will be held in Sydney at a date to be fixed.

Out of the Past.

In this column will be published from time to time extracts, taken from medical journals, newspapers, official and historical records, diaries and so on, dealing with events connected with the early medical history of Australia.

THE PRINCE ALFRED HOSPITAL.¹

[From *The Australasian Medical Gazette*, March, 1885.]

THE Directors of the Prince Alfred Hospital Sydney have arranged with the Senate of the University and the Medical Board of the Hospital a course of hospital clinical study in accord with the University curriculum and 14 students have entered their names on the Hospital books. The experience of the last 3 years shows that the cases admitted for treatment are of a type unusually well adapted to afford clinical instruction in the various branches of medicine and surgery, while the facilities available for teaching and study are already numerous and will be complete when the operation and speciality building is finished. The hospital now contains wards for diseases of women and children, for diseases of the eye, an operating theatre, four special wards for serious operations and a clinical lecture room. The Directors having, in a communication to the Royal College of Surgeons England, stated the number of beds and the opportunities for clinical study in the hospital and requested the recognition of the hospital for the purpose of qualifying for the diplomas of the College have received the following reply:

Lincoln's Inn Fields,
January 5, 1885.

Sir,

I have submitted to the Council your letter of September 27 last on behalf of the Board of Directors of the Prince Alfred Hospital Sydney New South Wales requesting the recognition of the hospital by the College and am desired to acquaint you that the Council have resolved that the Prince Alfred Hospital Sydney be added to the list of colonial hospitals recognized by the College.

I am, Sir,
EDWARD SUMMER,
Secretary.

¹ From the original in the Mitchell Library, Sydney.

Correspondence.

"A GUIDE TO BLOOD TRANSFUSION."

SIR: The New South Wales Division of the Australian Red Cross Society has published a small book entitled "A Guide to Blood Transfusion", by R. J. Walsh and H. K. Ward. The book is intended by the authors to meet the requirements of Australian medical students, general practitioners and others who administer blood transfusions, but who do not need the detail provided by larger reference books on the subject.

We are making this book available at its cost to us, and the authors will receive neither royalties nor fees. It is obtainable from the New South Wales Red Cross Blood Transfusion Service, 1 York Street, Sydney, at fl. To avoid opening accounts, it is requested that intending purchasers forward their remittance when ordering.

Yours, etc.,

A. M. MCINTOSH,
Chairman, Blood Transfusion
Committee.

Australian Red Cross Society (New South Wales Division),
Blood Transfusion Service,
1 York Street,
Sydney.
June 26, 1957.

SMOKING AND LUNG CANCER.

SIR: The report of the Medical Research Council of Great Britain on the serious consequences of the pleasant habit of tobacco smoking merely confirms facts which have already been established beyond doubt for some years. Had health authorities a quarter of a century ago taken cognizance of the first clinical observations on the apparent relationship between bronchitis, lung cancer, heart disease and the habit of smoking, and had they made the necessary statistical investigations to confirm them, the use of tobacco would by now have been reduced to an insignificant level. A substantial proportion of the one million deaths from lung cancer from this cause, which it is estimated will occur in Great Britain between now and the end of the century, might have been prevented.

It is to be hoped that in Australia these findings of the Medical Research Council of Great Britain, and the considered opinion, based on the reported data, of the National Health and Medical Research Council, will be accepted, and that this country will be to the forefront in taking active measures to eliminate the tobacco habit, especially among the young. It is also to be hoped that the medical profession will play a leading part in promoting any such measures—and to this end it appears that the following programme might be supported:

1. The prohibition of smoking in all public places of entertainment, in all public transport (except in the smoking compartments provided on trains), in shops and in those offices and business premises entered by the public.
2. The prohibition of smoking under the age of twenty-one.
3. The prohibition of any advertising of tobacco products in the Press or in public places.
4. The prohibition of any raising of capital for the purpose of promoting or expanding any company engaged wholly or in part in the manufacture of tobacco products or their wholesale or retail distribution.
5. The imposition of an additional and substantial tax on tobacco products, the proceeds of which would be specifically reserved for the creation of a national medical research fund, the objects of which would provide grants for research into all aspects of public health.
6. The promotion of a prolonged and intensive educational campaign to inform all persons, and in particular young subjects, of the serious dangers that are unfortunately associated with the tobacco habit.

Were it to be known that a substance was present in a food product that caused 10% of regular consumers to die of carcinoma of the stomach, there is no doubt that the use of that substance would be prohibited immediately and drastic penalties imposed on its continued sale. It is difficult therefore to understand the dilatory attitude of all concerned, health authorities in particular, to the established

dangers of the use of tobacco. The growth of the leaf is a waste of land; the manufacture of cigarettes, pipes and the miscellaneous paraphernalia so dear to the heart of the confirmed addict is a waste of labour; the purchase of these things by the public is a waste of money. It is to be hoped that the medical profession, having already, for no good reason, delayed too long, will now use the full force of its great influence in such matters to ensure that adequate steps are taken to eliminate this important cause of disease.

Yours, etc.,

ORDE POYNTON, M.D.

Institute of Medical and Veterinary Science,
Frome Road,
Adelaide.
July 2, 1957.

SIR: Cigarettes are blamed for endarteritis, peptic ulcer, coronary disease, cancer of lung, laryngitis. Surely a bit much even for the seductive coffin nail! The statisticians and the non-smokers never comment on the falling incidence of cancer of the tongue, pharynx and larynx. Could it be that smoke gets in the eye?

Yours, etc.,

"70 AND 70 A DAY".

Brisbane,
July 8, 1957.

THE EARLY TREATMENT OF SQUINT.

SIR: Some of the matters raised in Dr. K. O'Day's letter to you (M. J. AUSTRALIA, June 15, 1957) call for comment.

The child with the congenitally amblyopic eye should not have such an ordeal in the hands of the oculist. With a knowledge of the family history and the child's refraction, this should be suspected, even though, as is usually the case, no macular lesion can be discovered. Continuous or intermittent atropinization is a very useful policy to adopt until the child is old enough to obtain some guide to the visual acuity. A test period of a few weeks of total occlusion is then long enough.

Full binocular vision is not necessary to keep the eyes straight. Lyle and Foley (1955) have shown that peripheral fusion may be an important factor, and cite cases where fusion was apparently obtained and maintained when the vision of the poor eye was down to 1/60 only. It might appear, therefore, that if peripheral fusion is accepted, occlusion need not be pushed too long before operation. When an eye has no perception of light and there is no muscle paresis, ultimate divergence is almost certain.

The condemnation of orthoptic treatment is far too sweeping. The excellent results now being obtained from the surgical treatment of paralytic strabismus are, in many cases, due to the uncanny skill of the orthoptist who can produce a Hess chart from a pair of partially suppressing eyes. Orthoptics is in a state of extreme fluidity, and Lyle's later research work has rendered quite an amount of the material in his recent book "Practical Orthoptics" obsolete. General medicine is, however, in much the same position. The emphasis now is more on diagnosis and research and less on repetition work, and I have not yet had the misfortune to find an orthoptist who wasted her time on non-productive exercises. Her duty is to give a detailed account of the status of binocular vision, a record of the visual acuities and the angles of horizontal and vertical deviations. The onus for determining whether repetition work should be initiated or persisted with rests squarely on the oculist. Fortunately the position is now much clarified by the later work of Lyle and Foley (1957) as quoted by Dr. O'Day. In the completely accommodative type it is rarely required. In the partially accommodative types, simple exercises in the overcoming of suppression and in training to divorce accommodation and convergence appear to be very valuable.

The position in the case of the squinter of early origin—neither accommodative nor apparently parietic—is still obscure, and the ultimate results of surgery are often not inspiring.

Future progress in the treatment of the squinting child lies very much in the hands of the research team of oculist and orthoptist, and this requires the painstaking classification of cases and the results of treatment after protracted periods. Much reported work is valueless owing to poor classification of material. It can be done only in the larger hospitals, and the results are but slowly obtained. Every-

day unanswered problems which call for investigation include: (i) What place does surgery play in the treatment of the non-accommodative, non-paralytic squint? (ii) What prospects are there of obtaining binocular vision if the infant born with an apparent paretic muscle has his eyes straightened by operation in the first year of life? (iii) What is the safe angle of squint to leave in a child with reasonable binocular vision? (iv) What can be done for abnormal retinal correspondence when it now appears that the results of orthoptic treatment and surgical correction are alike unsatisfactory?

Binocular vision often remains an ideal—possibly at times somewhat of a fetish. Alternating vision with reasonable visual acuity is not far behind, and in the majority of cases, if the oculist can get this aided by a little very conservative cosmetic surgery, he should be well content.

I agree that bandaging and hospitalization can be overdone. However, if Dr. O'Day has such faith in the integrity of his sutures, why bandage at all?

Yours, etc.,

J. E. THOMAS.

Sturt Street,
Ballarat,
Victoria.
July 5, 1957.

References.

- LYLE, T. K., and FOLEY, J. (1955), "Subnormal Binocular Vision with Special Reference to Peripheral Fusion", *Brit. J. Ophthalm.*, 39: 474.
LYLE, T. K., and FOLEY, J. (1957), "Prognosis in Cases of Strabismus with Special Reference to Orthoptic Treatment", *Brit. J. Ophthalm.*, 41: 129.

THE L.E. PHENOMENON IN RHEUMATOID ARTHRITIS.

SIR: The L.E. phenomenon is regarded by most physicians as a reliable diagnostic test for disseminated *lupus erythematosus*, although it is known to be positive occasionally in other conditions. The observation by Parr, Shipton, Benjamin and White that L.E. cells were found in so many as 35 out of 55 cases of rheumatoid arthritis is truly surprising, and the statement that they were found on the first examination is indeed remarkable. Critical evaluation of the article and confirmation by other workers are essential before these results can be accepted.

The clinical findings appear straightforward. The diagnosis of rheumatoid arthritis is not a difficult one to make, although occasionally disseminated lupus may masquerade as rheumatoid arthritis for some time.

With regard to the pathological findings, strong exception must be taken to the fact that the method used for identifying L.E. cells was not described, and that there was no reference to control studies performed on normal subjects. Under these circumstances, technical fallacies are by no means excluded, and one feels that the article would be of more value if the L.E. phenomenon had been confirmed on these patients by other observers.

In contrast to the above article, one was impressed by the detailed description by Cowling and Thomas of the methods used to demonstrate the L.E. phenomenon, and the results obtained by these observers are far more convincing.

Yours, etc.,

IAN S. COLLINS.

311 Marrickville Road,
Marrickville,
New South Wales.
July 4, 1957.

THE RENAISSANCE OF GENERAL PRACTICE.

SIR: The article under the above heading in the *British Medical Journal* of May 11, 1957, by John H. Hunt, D.M., M.R.C.P., must not be allowed to pass without some complimentary remarks from Australia. May I commend it to all general practitioners in this country as a most refreshing document, which will give sustaining encouragement to all. After thirty-six years in general practice, I had been inclined to wonder whether the days of the old family doctor were not fast being numbered.

You will recall my rather wistful query on page 6 of "The Changing Face of Medical Practice: Retrospect and Prospects" as to what the future of the general practitioner really was. Dr. Hunt answers the inquiry in no uncertain manner when he declares that: "We are living in exciting times for the medical profession, academically and politically. . . . We inherit from our predecessors a better concept of the art of family doctoring than any other country in the world; and a great responsibility rests on us all—doctors, laymen, and politicians alike—to ensure that here and throughout the Commonwealth the present opportunity is seized to regain for general practice its rightful place as one of the finest branches of our profession and one of the most interesting and satisfactory in which to serve."

His remarks regarding the College of General Practitioners and research by general practitioners are very stimulating, and when after all the general practitioner is still 80% of the profession, it remains surely in our own hands to exert the pressure to see to it that post-graduate work, hospital work, and also medical literary work go on by the rank and file of the profession, whilst not in any way losing sight of the inestimable value of specialists, in their own sphere, and professors and teachers of particular subjects, and also the British Medical Association in its official capacity.

To close these remarks, I feel we must be ever on the alert to observe the political developments which are at this present moment touching our profession so vitally, more particularly in Great Britain, but also through the World Health Organization and the World Medical Association.

It cannot be overlooked that forms of regimentation, and in some countries, the worst forms of bureaucracy, would engulf medical practice in 100% government service.

The service we give under our present regime will be judged politically, and other countries are taking particular note of the Australian form of medical practice.

It behoves us to exploit group practice, foster closer general practitioner-specialist relationships, and handle the hospital benefit and medical benefit societies with the most scrupulous care, so that the evolving system will give the maximum service to the community, and enable anomalies to be ironed out, rather than any breakdown should occur. The alternative is some reversion to a free type of medical service, along the lines of the British or New Zealand capitation system.

One feels the profession should at this stage get wholeheartedly behind the idea of national insurance on a contributory basis, so that there will be some form of superannuation for all, and pension benefits will accrue to 100% of the community, with medical coverage at a high rating.

Let us hope that the Minister of Health will be able to broaden the benefits, and extend the cover, to take in increasing sections of the community, thus extending private practice, when the renaissance advocated by Dr. Hunt will become an accomplished fact and not a pipe dream. Banish the thought that we shall ever finish up as filing pigeon-hole experts, form fillers and medical sorters! May the College of General Practitioners flourish, and general practice enjoy an unprecedented revival.

Yours, etc.,

17 Boulder Road,
Kalgoorlie,
July 9, 1957.
H. T. ILLINGWORTH, M.B., Ch.M.

ELECTROENCEPHALOGRAPHIC EVIDENCE OF PERSONALITY CHANGES PRODUCED BY ATARAXIC DRUGS IN MENTALLY DISTURBED PATIENTS.

SIR: In his article of July 6, K. Andermann added further conjectures on the relation between known elements of electroencephalographic tracings and personality variables. However, as in many previous studies in this field, there are methodological lapses which lessen the value such work may have for psychological medicine.

Firstly, it is inferred that the clinical response to the ataraxic drugs may be predicted from certain alterations in alpha activity when these drugs are used as a sedative at the time of recording. The hypothesis is formulated on the evidence from eight cases using reserpine, three using benactazine, and one each of "Pacatal" and chlorpromazine. It might be questioned whether the lumping together of

these drugs is justified, since there is evidence that they are dissimilar in physiological and clinical effects.

Secondly, it seems pertinent that the criterion for change in alpha activity has been taken from the temporal region in the cases later showing clinical improvement, and from the parieto-occipital and frontal regions in at least three of the remaining cases, since no temporal record was available for these cases. This change of criterion appears all the more pertinent, as Table I of the same article shows that it is from these latter areas that little or no change can be expected.

Thirdly, any correlation would have been more impressive if the changes in the psychiatric state of the patient had been shown to be concomitant with the electroencephalographic changes and not estimated some considerable time after the recording. Moreover, correlation is a relative term, and some indication of its direction and magnitude might indicate whether further investigation is warranted. The failure to use statistical measures of significance is dangerous when working with such "easily interpreted" material.

Finally, the author appears to place some weight on the work of Saul and Davis relating alpha rhythm to certain aspects of the personality and the fact that similar relations have been mentioned by other workers. He points out that Ellingson states in his 1956 article that the relation is now generally accepted. That this is not, or should not, be the case is pointed out in the same article, where Ellingson quotes from his critical review of such studies made with Sisson, in 1955, that they "reviewed the evidence upon which that proposition was based and found it unconvincing". They also concluded that "no study has been done conclusively showing a relationship between any feature of the normal adult EEG recorded under standard conditions and any personality trait or variable". I feel that an impartial attitude would force us to the conclusion that this is still the case.

Yours, etc.,

July 9, 1957.

KEVIN W. WALSH.

Reference.

SISSON, B. D., and ELLINGSON, R. J. (1955). "On the Relationship Between 'Normal' EEG Patterns and Personality Variables", *J. Nerv. & Ment. Dis.*, 121: 353.

CONTACT DERMATITIS FROM 18-CARAT GOLD.

SIR: In your journal of July 6, 1957, Dr. Ernest Chenoweth reported a case of contact dermatitis from a gold wedding ring. It would be interesting to learn of the patient's domestic situation at the time the rash appeared, as one feels that psychogenic factors concerned with the symbolism of the ring could be involved.

Yours, etc.,

14 Parliament Place,
Melbourne,
July 10, 1957.

BRUCE ROBINSON.

Obituary.

ALAN WORSLEY HOLMES A COURT.

We are indebted to Dr. K. B. Noad for the following appreciation of the late Dr. Alan Worsley Holmes A Court.

Dr. Alan Worsley Holmes A Court, a Past President of The Royal Australasian College of Physicians, Consulting Physician to Sydney Hospital, and a very distinguished physician, died on April 16, 1957. His origin and career were alike of distinction. The name A Court is of old French derivation and was the name of the first Lord Heytesbury. After the marriage of an heir to the title with a daughter of Sir Leonard Worsley-Holmes, the name A Court-Holmes was taken. In 1860 this was changed by Royal Licence to Holmes A Court. Alan Holmes A Court was a grandson of the third Baron Heytesbury, and was born in Brisbane on June 19, 1887. He was educated at Brisbane Grammar School, and commenced his medical course in Sydney in 1906, graduating M.B. in 1910. He entered Sydney Hospital as a resident medical officer in 1911, and so began an association with that institution which he loved and served well for thirty-six years. It was apparent at once to his

fellow residents that he was marked out for distinction. "Whoever is to acquire a competent knowledge of medicine", said Hippocrates, "must bring to the task a love of labour and perseverance." Holmes A Court worked much harder and read more than his colleagues, and showed quite early the clinical acumen and infinite capacity for taking pains which were to characterize the whole of his medical career. Promoted registrar in 1912, he left the hospital at the end of that year and entered general practice in Manly. An appointment to Sydney Hospital as honorary assistant physician in 1914, only a year after completing his house-staff appointments, reflected the impression he had made.



Joining the Australian Army Medical Corps early in 1916, Holmes A Court received his first posting to Number 1 hospital ship *Karoola*. An incident from this period of his service may be cited as an instance of his clinical capacity and original mind. In August, 1917, the ship had anchored for four days at Sierra Leone, too far off shore, it was thought, for malaria to be a problem. About ten days after leaving, cases of fever and vomiting began to appear, and continued till 35 patients were in hospital. This epidemic baffled diagnosis till Holmes A Court was asked to investigate it. He examined blood films at once, and quickly established the diagnosis of subtertian malaria. His clinical and technical skill was to be exercised to a much greater degree in France in 1918, with the splendid work he did while in command of the resuscitation team attached to the Australian Army Medical Corps. "There can be no room for doubt", wrote the Acting Consulting Surgeon Fourth Army, Major G.—now Sir Gordon—Gordon-Taylor, "that very many lives have been saved by the work of Major Holmes A Court and the members of the other resuscitation teams." The same officer and Sir Anthony Bowlby, Senior Consulting Surgeon, British Expeditionary Force, were amazed to find one man, who had received a piece of shrapnel in the neck which had lodged in the carotid artery, sent back after ligation of the vessel by Holmes A Court. They came up to the field ambulance to see who had met the emergency so capably. After doing much work of this kind during that year, and being naturally dexterous, Holmes A Court seriously considered at one stage taking up surgery. In later life he always liked to help at operations upon his patients, and was recognized as a most skilful assistant. For his work in the field he was promoted lieutenant-colonel, mentioned in dispatches and awarded the *Médaille des épidémies (en argent)*. After the Armistice, Holmes A Court proceeded to London, where in 1919 he passed the examination for membership of the Royal College of Physicians of London. He was elected to Fellowship of the College in 1930.

Returning to Australia in 1919, he began practice in Macquarie Street, and rapidly acquired a reputation as a consultant. He proceeded to the degree of M.D. (Sydney) in 1920 with a thesis on "Intravenous Injections in the Treatment of Haemorrhage and Shock", which embodied the results of his observations during his great work in France. Becoming an indoor physician at Sydney Hospital in 1923, Holmes & Court soon gave evidence of his interest in the clinical work of the hospital. In association with Dr. George Bell, the first blood transfusions were given by the whole-blood Kimpton tube method. Holmes & Court was instrumental in the improvement of anæsthetic methods in the hospital, and responsible for the formation of the Sydney Hospital Clinical Society. He was enthusiastic in the teaching of students. His clarity of mind, precise economical speech, clinical flair and wide experience made his rounds memorable occasions. Appointed clinical lecturer in 1931, he took infinite pains to make his lectures essentially practical and a distillate of his own experience. He preferred to demonstrate patients at the beginning of each lecture and use them as a text for a clinical talk illustrated by carefully chosen slides. He retired from the active staff and became consultant in 1947.

Elected to the Council of the New South Wales Branch of the British Medical Association in 1925, he served for two terms, 1925 to 1929 and 1931 to 1935. He was president in 1933. The demands of a large consulting practice and hospital work led to his relinquishing membership of Council in 1935. His consulting practice had become very large, and he was acknowledged to be one of the leaders in medicine in Sydney. Holmes & Court took an active part in the Association of Physicians of Australia, the body from which The Royal Australasian College of Physicians arose. When the College was formed in 1938, he was a Foundation Fellow, and he became a member of the first Council and Executive Committee and served on these bodies till his death. He loved the College, and he served it faithfully and well as councillor, as a member of the Australian Board of Censors (1938 to 1945), as Censor-in-Chief (1945 to 1950), as President (1952 to 1954), and as chairman of the editorial committee of the *Australasian Annals of Medicine* from the foundation of the journal till his death. It was natural, with his background, that an affection for and interest in the parent College should remain with him. He was senior Fellow of the London College in New South Wales for many years, and his advice was frequently sought on matters pertaining to the College in this State. He was largely responsible for the visit to Australia and New Zealand of Sir Russell Brain in 1956. This was the first occasion on which a president had visited these shores during his presidency. All were agreed that it was a visit of the greatest value, not only to the Colleges of Physicians, but also in the wider sphere of Commonwealth relations. It gave the greatest satisfaction to Holmes & Court, who had done so much to bring it about.

His chief recreations were fly-fishing and yachting. He devoted about an equal amount of time to each in earlier years. He owned and occasionally raced *Brilliant*; but after the death of his elder son on service, his enthusiasm waned, and he sold the boat to devote his vacations to fishing. He frequently visited the waters of the southern alps with a congenial company of fellow anglers, with whom he regularly fished. He was the perfect companion on these expeditions, making light of the discomforts and vicissitudes which frequently beset such activities. He could also turn his hand to anything, and consequently was always the "handyman" of the party. After a morning's fishing, he loved to sit at midday absorbing the beauty of bird, bush and stream, and was wont to exclaim: "This is the hour of adoration!"

Mention must be made of his love for animals. "One comes to a time in life when one can't bear to hurt a fly", he once said. One is reminded of Plato's "Symposium", and Eryximachus saying: "Such is the conclusion which I seem to have gathered from my own art of medicine, whence I learn how great and wonderful and universal is the deity of love, whose empire extends over all things, divine as well as human." Dogs were a passion with Holmes & Court, and it was always a charming sight to see him surrounded by them. He understood dogs and they adored him. He was essentially reserved and rather a shy man, but always friendly, courteous and urbane in manner. He dressed with a quiet elegance, and the sight of his familiar figure will be missed from "the street" by his many friends.

Holmes & Court had led a full life and had graced the practice of medicine, his hospital, the College, everything

with which he was associated. He was most generous and helpful in a practical way, as well as with advice, to young men aspiring to the practice of medicine. Many who have achieved success can look back with gratitude to the help he gave them when they were starting. Sydney has lost one of its "names" in medicine, and the profession will be the poorer for his death. Throughout his life he was loyally supported by his wife, whom he married in 1913. She provided the background of a lovely and happy home, in which it gave him the greatest pleasure to entertain his many friends. To his widow, daughter and son we extend our deep sympathy.

DR. D. G. MAITLAND writes: The medical profession and the community suffered a very great loss at the sudden death of Alan Holmes & Court on Tuesday afternoon, April 16, soon after he had been admitted to Sydney Hospital, and perhaps it was fitting that his very full and active life should have ended in the hospital where so much of his professional life and interest had been centred since his graduation from the University of Sydney Medical School in 1910. His death has left a gap in the medical life of Sydney which many of us feel will never be quite filled.

Others will have recorded his outstanding academic achievements, his sterling services during the 1914-1918 war and his remarkable ability and promise as a young surgeon, before he made the decision to concentrate his energy in the awakening and expanding scientific field of medicine as a consultant physician. Others will have recalled his years of association with the New South Wales Branch of the British Medical Association, of which he became President in 1933, and also will have mentioned the formation of The Royal Australasian College of Physicians—of which he was elected its President in 1950.

Alan Holmes & Court had perhaps as his most salient characteristic, kindness. To his patients he radiated confidence and strength, and when he knew that there was nothing more that medical science could do to aid, he gave, with his verdict, both sympathy and understanding. It is a hard task to attempt to put into words the memory of the twinkle in the eye, the droll humour which endeared him to his students and confrères, the immaculate and distinguished figure; yet he was never unapproachable, and always gave a helping hand to the "young ones coming on". He had many outside interests, which included yachting and the art of trout-fishing; but no matter what his interests were, he carried them out with great ability and skill by the application of practical and acquired knowledge, for his memory of literature and events was an almost photographic one.

We met soon after the death of my father in May, 1923, when I was a first-year medical student, and that meeting proved to be the beginning of a very close and treasured friendship of later years. His family and home meant much to him, and the loss of his elder son Brian, who was a "Spitfire" pilot during World War II, was a severe blow. He possessed a great personal dignity and charm, a calm and even manner, sound wisdom, foresight and judgement, and a keen appreciation of correct procedure—all of which commanded respect, and endeared him to his many professional associates and friends.

Looking back over the years, I am fully conscious of the guidance, help, friendship and trust which have been my privilege since 1923, and there are many members of the medical profession, both young and old, who will join me in offering sympathy to his wife, daughter and son, and in recording a sincere appreciation of a kindly counsellor, a true friend and gentleman.

SIR ALEXANDER MURPHY writes: Alan Holmes & Court was a man of high principle, rare charm, and beloved of all who really knew him. Although by nature somewhat reserved, his love for his chosen profession and strong sense of duty led him to great eminence, not only as a physician, but also in the service of the institutions complementary to medicine. Honorary physician at Sydney Hospital, President of the New South Wales Branch of the British Medical Association and later of The Royal Australasian College of Physicians, he filled these positions with dignity and distinction. As Censor-in-Chief of the College he was affectionately known to his colleagues on the Board as "Master", and his unflagging efforts to establish and maintain a high standard in this, as in all his other activities, will long be remembered. He tempered justice with kindness and humour, his integrity was unchallenged, and he scorned the hypocrite and the intriguer. A well-read man with an excellent memory, he had a wide knowledge of the poets and loved the lift of verse; but his greatest delight was to be at the helm of his

yacht like a Viking of old, "The salt wind wet on his helmet wings", with ear tuned to the cadence of the sea.

Grief at the loss of his eldest son in the Air Force in the second World War was his constant companion; but characteristically this was concealed from all but a few of his most intimate friends.

He died as he would have wished, "The steering oar of the running ship in his hands", and Australian medicine, the College that he loved and served so well, and many people have suffered irreparable loss.

Of my old friend I would say in the words of Hamlet:

He was a man, take him for all in all,
I shall not look upon his like again.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Annual Subscription Course.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that Mr. A. Dickson Wright, F.R.C.S., D.T.M. and H., Surgeon to St. Mary's Hospital and to the Prince of Wales Hospital, London, and Honorary Treasurer of the Imperial Cancer Research Fund, will visit Sydney from August 2, 1957. Mr. Dickson Wright will give the following lectures at the Stawell Hall, 145 Macquarie Street, Sydney, at 8.15 p.m. on the dates stated: "Varicose Veins", Wednesday, August 7; "Simplification of Biliary Surgery", Thursday, August 15; "Intestinal Obstruction", Wednesday, September 11 (arranged in conjunction with the New South Wales State Committee of the Royal Australasian College of Surgeons).

The following programme has also been arranged:

"Ulcerative Colitis": Sydney Hospital, Wednesday, August 7, at 2.15 p.m.; St. Vincent's Hospital, Tuesday, September 3, at 10 a.m.; Royal Prince Alfred Hospital, Tuesday, Sep-

tember 10, at 8 p.m.; Lewisham Hospital, Wednesday, September 11, at 10 a.m.

"Varicose Veins": The Royal Newcastle Hospital, Friday, August 9.

Film, "The Painful Arm": Royal Prince Alfred Hospital, Monday, September 9, at 8 p.m.

Mr. Dickson Wright will be Guest Professor at The Royal North Shore Hospital during Reunion Week, beginning on Monday, August 12. His programme will include the following lectures, which are open to members of the annual subscription course: Tuesday, August 13, at 3.30 p.m., "Varicose Veins"; Thursday, August 15, at 2.15 p.m., "Ulcerative Colitis".

Post-Graduate Conference at Newcastle.

The Post-Graduate Committee in Medicine in the University of Sydney announces that, in conjunction with the Central Northern Medical Association, the medical section of the 1957 post-graduate conference will be held in the Lecture Theatre, Royal Newcastle Hospital, on Saturday and Sunday, August 17 and 18, 1957. The programme is as follows:

Saturday, August 17: 2.30 p.m., registration; 2.45 p.m., "Respiratory Emergencies, Including Respiratory Obstructions, Status Asthmaticus and Spontaneous Pneumothorax", Dr. D. G. Hamilton; 4.15 p.m., "The Management of Some Cardio-Vascular Emergencies", Dr. George V. Hall.

Sunday, August 18: 10 a.m., "(a) The Convulsing Child: Status Epilepticus, (b) Severe Gastro-Enteritis, (c) Meningococcal Septicemia", Dr. D. G. Hamilton; 11.30 a.m. to 12.30 p.m., "Aortic Stenosis: A Surgical Disease", Dr. George V. Hall.

The 1957 post-graduate conference at Newcastle is divided into three sections: (i) gynaecology and obstetrics (April 27 and 28), (ii) medicine (August 17 and 18), (iii) surgery (November 23 and 24).

The combined fee for attendance is £3 3s., or £1 1s. for each section. Those wishing to attend are requested to notify Dr. J. N. Walker, Honorary Secretary, Central Northern Medical Association, 22 Church Street, Newcastle, as soon as possible. Telephone: Newcastle B 1201.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED JULY 6, 1957.¹

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	5	1	5(4)	4(4)	1(1)	16
Amoebiasis	2(2)	2
Ancylostomiasis	1	..	2	3
Anthrax
Bilharziasis
Brucellosis
Cholera	1	1
Chorea (St. Vitus)
Dengue
Diarrhoea (Infantile)	28(28)	1(1)	1	30
Diphtheria	3	1	4
Dysentery (Bacillary)	1(1)	1	2
Encephalitis	1(1)	2(2)	3
Filariasis
Homologous Serum Jaundice
Hydatid	1(1)	1
Infective Hepatitis	57(26)	59(51)	3(3)	2(2)	10(6)	9	1	..	141
Lead Poisoning
Leprosy	1	1
Leptospirosis	9(1)	9
Malaria	1(1)	1
Meningococcal Infection	2(1)	3(2)	4	..	1(1)	1	11
Ophthalmia
Ornithosis
Paratyphoid
Plague
Poliomyelitis	1(1)	1	2
Puerperal Fever	2	2
Rubella	29(24)	..	53(11)	1(1)	83
Salmonella Infection	7(5)	5(4)	2(2)	1	55
Scarlet Fever	15(10)	25(18)
Smallpox	1	1
Tetanus	6(2)	6
Trachoma
Trichinosis
Tuberculosis	24(19)	13(9)	36(27)	5(4)	4(1)	3(2)	85
Typhoid Fever	1	1
Typhus (Flea-, Mite- and Tick-borne)
Typhus (Louse-borne)
Yellow Fever

¹ Figures in parentheses are those for the metropolitan area.

THE MELBOURNE MEDICAL POST-GRADUATE COMMITTEE.

PROGRAMME FOR AUGUST, 1957.

THE following addition to the programme for August, 1957, has been forwarded by the Melbourne Medical Post-Graduate Committee.

Demonstration at the Eye and Ear Hospital.

On Saturday, August 24, 1957, from 9.30 a.m. until 12 noon, the staff of the Victorian Eye and Ear Hospital will hold a clinical demonstration of eye, ear, nose and throat conditions commonly encountered in general practice. This is an addition to the general refresher course, and is open to all members of the medical profession who wish to attend.

The Royal Australasian College of Physicians.

EXAMINATION FOR MEMBERSHIP.

THE next examination for membership of The Royal Australasian College of Physicians will be held on the following dates: written examination (capital cities), Friday, August 30, 1957; clinical examination (Sydney), commencing on or about Thursday, October 10, 1957.

Application forms may be obtained from the Honorary Secretary, 145 Macquarie Street, Sydney, and applications should be lodged with the Honorary Secretary not later than Friday, August 2, 1957.

Royal Australasian College of Surgeons.

OPEN MEETING.

THERE will be a meeting of the Royal Australasian College of Surgeons in the Stawell Hall of The Royal Australasian College of Physicians, 145 Macquarie Street, Sydney, on Wednesday, July 31, 1957, at 8.15 p.m. (not on July 24 as previously arranged). The programme will be as follows: "Use of Intestinal Transplants", Mr. K. W. Starr, Mr. K. Kirkland (opener); "Intestinal Anastomosis", Mr. J. W. Graham, Mr. K. S. Jones (opener). This meeting is open to all medical practitioners.

Notice.

SPECIAL GROUP ON AVIATION MEDICINE.

THE Special Group on Aviation Medicine (British Medical Association) will hold a meeting at 49 Mathoura Road, Toorak, Victoria, on Thursday, August 8, 1957, at 8 p.m. Mr. Douglas G. Humphries will speak on "Recent and Future Developments in Aircraft Performance", and will indicate some flight crew problems which arise. Mr. Humphries is at present Chief Designer at the Commonwealth Aircraft Corporation. Members of the British Medical Association and guests of members would be welcome.

CLINICAL BIOCHEMISTRY MEETINGS.

A MEETING for those interested in clinical biochemistry will be held in the Scot Skirving Lecture Theatre, Royal Prince Alfred Hospital, Sydney, on Wednesday, August 7, 1957, at 7.15 p.m. The subject will be "Liver Function Tests", and the speakers will be K. Mattocks, M.B., B.S. (Royal Prince Alfred Hospital), F. J. Radcliff, B.Sc. (Royal North Shore Hospital), and D. Rothfield, M.B., B.S. (St. Vincent's Hospital).

A second meeting is being arranged for early September, and will be the subject of a further notice. On this occasion the subject will be "The Estimation of Steroids and Some Aspects of the Clinical Significance of These Tests", and the speakers will be B. Stacey, Ph.D. (Sydney Hospital), and R. I. Cox, Ph.D. (veterinary physician, University of Sydney).

A third meeting is envisaged for October, at which it is hoped to discuss and form a group or society for graduates (science, medicine etc., including diplomates) interested in

clinical biochemistry. It is believed that there is scope in New South Wales for a society to promote the interchange of technical and scientific ideas and to provide a meeting ground for members of such a group.

The organizing committee is as follows: Miss E. A. Stobo (Royal Alexandra Hospital for Children), Dr. B. Stacey (Sydney Hospital), Dr. K. Mattocks (Royal Prince Alfred Hospital), Dr. D. Rothfield (St. Vincent's Hospital) and Dr. D. B. Morell (Royal North Shore Hospital), convener.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

- Campbell, Eric Charles, M.B., B.S., 1955 (Univ. Sydney), 20 Kellett Street, Kings Cross, New South Wales.
- Hillier, Doreen Elizabeth, M.B., Ch.B., 1951 (Univ. Bristol), Argent House, Argent Street, Broken Hill, New South Wales.
- Hillier, Geoffrey John, M.B., Ch.B., 1952 (Univ. Bristol), Argent House, Argent Street, Broken Hill, New South Wales.

Deaths.

THE following death has been announced:

CLARK.—Ernest Dagnall Clark, on July 9, 1957, at Lindfield, New South Wales.

Diary for the Month.

- Aug. 6.—New South Wales Branch, B.M.A.: Organization and Science Committee.
- Aug. 7.—Victorian Branch, B.M.A.: Branch Meeting.
- Aug. 7.—Western Australian Branch, B.M.A.: Branch Council.
- Aug. 9.—Tasmanian Branch, B.M.A.: Branch Council.
- Aug. 13.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

Queensland Branch (Honorary Secretary, 88 L'Estrange Terrace, Kelvin Grove, Brisbane, W.1): All applicants for Queensland State Government Insurance Office positions are advised to communicate with the Honorary Secretary of the Branch before accepting posts.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

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